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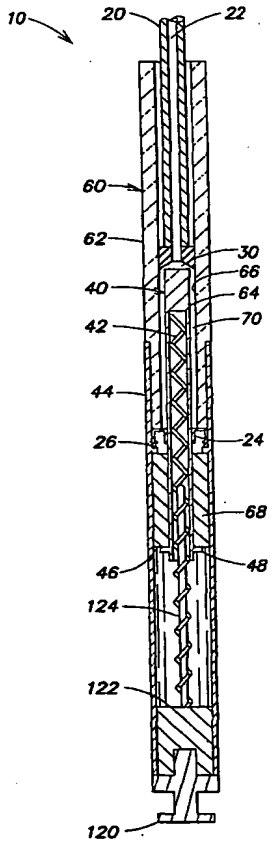
(54) Title: DUAL RESOLUTION SYRINGE



(57) Abstract: A syringe for accurately metering small volumes of fluid samples is provided with dual resolution capabilities. The syringe permits the aspiration of a tiny sample and also the dilution of a tiny sample with a much larger volume of reagent with the same syringe. The syringe also allows the aspiration of a minute fluid sample and the touchless transfer off the fluid sample from the tip of the syringe. The present invention allows the aspiration resolution to differ from the dispensing resolution. The dual resolution capabilities also permits the present invention to be implemented into existing conventional syringe drive system. The syringe may include a housing, a piston within the housing, and a plunger extending from the housing. A chamber is formed in the housing between the plunger and a sealing means and between the piston and the inner surface of the housing. The chamber may further include first and second portions, where the volume change of the fluid in the first and second portions corresponds to the dual resolution capabilities.

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DUAL RESOLUTION SYRINGE

BACKGROUND OF INVENTION

1. Field of Invention

The present invention relates to syringes which can accurately meter small volumes of fluid. In one embodiment, the syringe has dual resolution capabilities which enables the aspiration of a tiny sample and also the dilution of the tiny sample with a much larger volume of reagent (or another sample) with the same syringe.

2. Discussion of Related Art

In recent years, diagnostic and analytic tests have required smaller and smaller samples to be accurately metered, both to mix or dilute the samples with larger volumes of various reagents (sometimes in high dilution proportions) and to transfer them separately. There is a demand for samples less than 1 microliter and even less than 100 nanoliters or even 10 nanoliters to be aspirated and delivered using a syringe or pipette system. Unfortunately, positive displacement devices that can accurately pick up the minute volume of the sample cannot provide enough flow to completely transfer the sample and cannot also meter large reagent volumes. Often times when transferring the sample, the sample will hang onto the tip of the syringe, which requires touching the sample to another surface to free it from the capillary action and surface tension. A touchless transfer, where the sample is ejected out of the syringe with enough force to prevent the sample from hanging on the tip of the syringe, is desired. One way to increase the ejection force of a syringe is to use a syringe with a larger diameter. Yet when the diameter of a syringe is increased to prevent the "hanging drop" occurrence, the accuracy of the size of the sample aspirated is compromised. While a larger diameter syringe can effect a touchless transfer, it cannot precisely aspirate a tiny sample, such as one as minute as 10 nanoliters.

Multiple pistons of different diameters contained within a single pipette chamber or cylinder such as described below have been known in the past. In such pipettes, spring means are used to keep the pistons in an upper position with a thumb-pressed button so that the pistons can be moved against the force of helical springs to a pre-

determined lower position. These systems have been used for a variety of purposes, including the transfer of small volumes of fluids.

In Patent No. 5,383,372, assigned to DRD Diluter Corporation, a design is provided with a plurality of pistons that move together and separately in a pipette chamber to measure a small sample and then dispense it with an air blowout to completely remove the sample. While these systems have provided the capability of dispensing small samples with some significant air blow-off or touchless transfer, the demand for using smaller and smaller samples require systems and devices which permit the aspiration and ejection of smaller and smaller samples. These requirements become more acute with the development of programs for genetic testing of patient's blood and blood derivatives. Minute aspirations of less than 100 nanoliters and often even 10 nanoliters are now becoming important.

In many instances, it is desirable to deliver the samples by a "touchless" system that does not require the samples to be touched by another surface, washed out by another liquid, or delivered beneath the surface of another liquid. Therefore new delivery and syringe means are required. Satisfying these developing requirements has been difficult because drops tend to hang onto the tip of the delivery tube forming a hanging drop. The size of the hanging drops can vary widely, and syringes or single piston devices with resolution fine enough to pick up tiny samples simply do not have the flow power to cleanly blow off the sample. A typical sample must be given a velocity when leaving the tip of the probe or pipette of at least approximately 1 meter per second to break free. The smaller the sample, the greater the inaccuracy caused by a hanging drop remaining on the syringe tip. For a variety of reasons, this escape velocity is particularly difficult to achieve with the very small syringes needed to handle very small samples. The problem is further complicated by the requirement that these transfer devices or pipettes be useful for materials that have a widely varied viscosity, from blood derivatives like serum to chemicals like DMSO to various viscous genetic brews. The viscosity variation introduces further variations in the ability of a given sample to escape a confining tip.

Past efforts to achieve desired results involve the miniaturization of syringes to meter smaller and smaller samples. However, small syringes lack the flow power

necessary to expel tiny samples. Smaller and smaller probe and pipette tips were developed so that the lower flow rates and pressures the small syringes were able to deliver were artificially increased in an effort to achieve a tip escape velocity. Tips with internal diameters as small as 0.010 inches were developed and in recent years solenoid valve approaches have relied on sapphire drill channels as small as 0.002 inches to provide a sufficient velocity lift at the tip. These delivery tubes result in very long narrow columns of liquid passing through the syringe orifice, which exposes a significantly large proportion of the total fluid volume to damaging surfaces. As a result, genetically related assays which helped trigger the interest in smaller pipettes are compromised because the samples are damaged by the extensive surface area contact to which the assay material is subjected. Therefore, to prevent extensive surface area contact damage to the sample, it is beneficial to not use an excessively small probe tip.

The demand for means and methods for metering very small volumes of material with significant resolution is increasing the need for pumps and pipettes having the equivalent of 10 microliters syringe resolution power, with 1 microliters syringe resolution likely required in the future. These precise requirements for accurate dispensation of very small quantities of material present additional problems. For example, glass is a choice material because much diagnostic work benefits from clear glass for visual inspection. In addition, glass is chemically very inert. However, manufacturing glass tubes with very small internal diameters precise and accurate enough to achieve the equivalent of a 10 microliters traditional syringe is costly due to the small dimensions. Due to the rugged manufacturable larger sized components of the present invention, the prior problems associated with manufacturing tiny syringes is obviated.

Furthermore, traditional syringes for metering small and minute volumes of fluid are troubled with sealing problems. Teflon seals are the industry standard due to its low coefficient of friction and Teflon is chemically inert. However, Teflon has the undesirable characteristic of a high coefficient of thermal expansion and its size can vary considerably with temperature. These slight changes in properties are negligible with a large syringe, but are physically noticeable with traditional syringes that can handles small volumes of fluid. At room temperature, a Teflon seal fit for the internal diameter

of a glass syringe can slide smoothly within the housing and seal inside. However at cooler or warmer temperatures, the Teflon seal can be too loose or too tight and "stick" therefore the piston cannot be moved as smoothly within the housing or the seal leaks. Since the present invention is able to achieve the resolution of a small syringe with larger components, thermal variations of the sealing material are enormously reduced with the present invention.

Additional concerns not only center on the need to meter smaller and smaller samples with finer resolution, but also there is an increasing need for a more efficient method and means for delivering the selected sample in its entirety without damaging it. As noted, systems used heretofore commonly attempt to solve this problem by adopting probes and tips with artificially small diameters intended to increase the tip velocity of the material being delivered. These efforts have resulted in mechanisms that have a ratio far in excess of 10:1 between the length of the sample streaming through the tip and the diameter of the sample, which means greater exposure of the material being delivered to surface contact. Applicant has found that if the height to diameter ratio of the sample in a probe or pipette tip is not greater than 10:1 the sample is likely relatively undamaged due to surface area contact. Furthermore, Applicant found that approximately 1:1 to 10:1 may be optimal for blowing or blasting off discrete samples cleanly without damaging them. Applicant has found for a sample as small as 20 nanoliters (0.02 microliters), for example, a probe that is 0.011 to 0.012 inches in internal diameter will support a stable slug of liquid with a healthy height to diameter ratio of 1:1 whereas a solenoid driven sapphire probe ID of 0.003 inches would require a column 80 times as tall as it is across. For samples in the 100 nanoliters-1 microliters range, a probe diameter of 0.016 to 0.022 inches is healthy and desirable to keep the sample height to diameter ratio roughly in the 1:1 to 10:1 range, but blowing off such a sample through such a healthy diameter probe with conventional techniques would require a syringe or plunger or piston much larger than could accurately meter or aspirate the sample.

Traditional single piston syringes used for aspirating minute samples are difficult to prime and keep clear of trapped bubbles. Due to the small volume of the fluid sample, a few tiny air bubbles in the chamber can cause a high percentage of measurement error. Furthermore, the tiny outwardly pressing wiper seals of traditional small syringes wear

out quickly. Efforts to get around these seal problems have led to using o-rings and compression seals through which a piston slides, however problems have arose due to the sizes involved. For example, a traditional single piston 100 microliters syringe has an inside diameter of only 0.057 inches (1.4 mm) and a 10 microliters syringe has an ID of only 0.018 inches (0.46 mm). Therefore, it is essentially like trying to seal a needle. The above mentioned sealing and bubble entrapment problems have led to development of non-positive displacement techniques such as piezoelectric technology and solenoids, but these tend to be expensive or require frequent timing-related calibration or are prone to clogging.

Further, the tiny ID of such small glass syringes are difficult to manufacture. The accuracy of measurement using a syringe is only as accurate as the tolerances involved with manufacturing. The present invention succeeds in addressing this problem by grinding or lapping the outer diameters of the piston rather than trying to control the inside diameter of the tubing. When the tubing is glass it is typically formed over mandrels. The best commercial glass tubing production technique for a 1 milliliter syringe cannot control the inside diameter better than +/- 0.0005 inches, or in extreme special cases down to +/- 0.0002 inches. However, using precise outer diameter grinding techniques, the present invention can control the OD to more than an order of magnitude greater. The Applicant has found that this precise grinding of the outer diameter of the piston can be done to match the measured ID of lots of glass tubing to produce a differential resolution as fine as a 1-10 microliter conventional syringe. For example, if one needed resolution as fine as a 10 microliters syringe, such as to aspirate 25 nanoliters, the conventional single piston syringe ID would need to be 0.01814 inches. This small size may be impractical for automated use. With the present invention, the same resolution may be accomplished with a glass tube with a practical sized ID of 0.1814 inches and a piston with an OD of 0.1804 inches. Without sacrificing resolution capabilities, the present invention includes practical sizes to work with and to manufacture.

Continuing with the above example, if the inside diameter of a manufactured lot of glass tubing was actually 0.1811 inches (rather than the intended 0.1814 inches) due to manufacturing variance, if undetected this could result in errors up to 20% in a dual

resolution syringe. However, with the present invention, one can compensate for the varied ID of the glass tubing lots by adjusting the grinding amount of the outside diameter of the piston. Grinding the OD of the piston to 0.1802 inches (rather than 0.1804 inches) will easily compensate for inherent variations in the manufacturing process of the glass. As explained in more detail below, because the present invention may use the difference in the cross-sectional areas between the glass chamber and the piston it not only permits practical minute volume resolution but it can also compensate for the sometimes relatively crude manufacturing tolerances of glass tubes.

SUMMARY OF INVENTION

The present invention overcomes prior limitations of conventional syringes that cannot accurately meter small volumes of fluid and/or that do not have dual resolution capabilities. Another feature of the dual resolution capabilities provided by the present invention is the ability to facilitate a touchless transfer of a fluid sample from the tip of the syringe. Furthermore, this invention permits positive displacement fluid metering technology to handle small samples along the order of magnitude of microliters (thousands of a milliliter) and even nanoliters (thousands of a microliter). The dual resolution feature also permits the aspiration resolution to differ from the dispensing resolution.

In one illustrative embodiment of the invention, a syringe is provided with dual resolution capabilities. The syringe comprises a housing with a chamber formed therein with a plunger and a piston movable within the housing. The volume of the chamber may vary by movement of the piston or plunger or housing. The chamber may further be defined by a first and a second portion of the chamber wherein the volumes of each portion may change independently of one another.

A method of transferring minute quantities of fluid is also provided, and in another embodiment a method of transferring multiple fluid samples from a single aspirated sample is provided.

In another illustrative embodiment, a syringe is provided operating only under differential capabilities. The invention also includes a device that is capable of diluting a minute sample with an external or internal reagent. Furthermore, the present invention

provides a method for metering fluid samples where the aspiration resolution differs from the dispensing resolution.

The present invention helps to overcome the existing problems with the prior art. The dual resolution syringe provides two modes where substantially different volumes of fluid can be metered. Through experimentation, it was found that a large Bulk Mode flow capacity like that of a 1 milliliter syringe in conjunction with a very fine Differential Mode resolution like that of a 10-100 microliters syringe is able to transfer 0.05-1 microliters liquid aliquot and then touchlessly transferring the liquid aliquot by utilizing an interposed air gap. This air gap is designed to be large enough to dispense the sample out of the syringe while in Bulk Mode. The dual resolution syringe picks up a tiny sample of approximately 1 microliters in the Differential Mode and then uses the Bulk Mode to touchlessly transfer the sample by ejecting the sample out of the syringe along with most of the preceding relatively large 10-15 microliters air gap. Or the dual resolution syringe picks up a minute 0.05 microliters (50 nanoliters) sample and similarly ejects it with most of a preceding relatively huge 2-4 microliters air gap. With the dual resolution syringe, the interposed air gap can be perhaps 1-15 microliters with an aspirated sample volume of 10 nanoliters to 1 microliters. In the present invention, the syringe size utilized in most of the examples provides a difference in the resolution of the two modes of operation of a factor of approximately 100, which was found desirable in experiments.

The present invention also facilitates high ratio dilution by the accurate aspiration of a minute sample combined with the aspiration or internal metering of a relatively large volume of a dilution fluid all by the same device. The volume of the dilution fluid will typically be at least 10 times greater than the volume of the sample. Prior art syringes that could meter the volume required by the size of the dilution fluid are not able to aspirate a minute sample with precision and accuracy. The dual resolution capability of the present invention enables the accurate aspiration and combination of widely different volumes of sample and diluent.

Furthermore, the present invention permits positive displacement fluid handling technology to be used in conjunction with samples in the microliter and nanoliter scale. "Positive displacement" simply means that a space-occupying mass or positive

displacement element, such as a piston, enters a fluid-filled space and displaces that fluid from the space in a volume equal to that of the positive displacement element that enters the space. Typical positive displacement syringes are limited in measuring smaller and smaller samples due to manufacturing tolerances, seal performance, and general size constraints. In one embodiment, the present invention utilizes the Differential Mode to successfully meter samples as small as 10 nanoliters, illustrating positive displacement fluid handling technology unhampered by previous size limitations associated with conventional syringes that do not exhibit differential capabilities.

Further the present invention is designed to readily be retrofitted into an existing conventional syringe drive system and module. Previous dual resolution designs, such as the previously discussed '372 patent, attempts required a completely new system of supporting hardware. The design of the present invention enables it to be configured and sized similar to conventional syringes and may be readily adaptable to and generally used directly in conventional single piston drive systems. This provides one with the ability to upgrade easily to a dual resolution syringe. There is a vast array of prior art conventional single piston syringes equipped with a drive system and module. With the present invention, one can take out the conventional syringe and replace it with the present invention and have a dual resolution syringe system because the present invention is compatible with the existing supporting hardware for conventional syringes. Additionally, the present invention is applicable to both reusable and disposable syringes.

BRIEF DESCRIPTION OF DRAWINGS

The accompanying drawings, are not intended to be drawn to scale. In the drawings, each identical or nearly identical component that is illustrated in various figures is represented by a like numeral. For purposes of clarity, not every component may be labeled in every drawing. In the drawings:

Figs. 1A and 1B illustrate the syringe in two selected positions in detail;

Fig. 2 illustrates a detailed view of the bracketed range in Fig. 1B;

Fig. 3 illustrates a tapered piston;

Figs. 4A-4C illustrate one embodiment of the syringe that operates in a Differential Mode;

Fig. 5 illustrates a syringe with associated surrounding equipment in one embodiment;

Figs. 6.1 – 6.5 illustrate the aspiration process;

Figs. 7.1 – 7.5 illustrate the dispensing process;

Fig. 8A illustrates escape velocity data for conventional single piston syringes;

Fig. 8B illustrates column height and ballistic stability ratios for conventional single piston syringes;

Fig. 8C illustrates the "blastoff" process;

Fig. 9.1-9.6 illustrates the application of diluting a sample with an internal diluent;

Fig. 10.1-10.8 illustrates the application of diluting a sample with an external diluent;

Fig. 11.1-11.6 illustrates the process of fluid sample pickup and touchless "blastoff" Transfer;

Fig. 12.1-12.9 illustrates repetitive touchless "blastoff" transfer from a single aspirated sample;

Fig. 13 illustrates a further alternative embodiment; and

Fig. 14 illustrates a further alternative embodiment.

DETAILED DESCRIPTION

This invention is not limited in its application to the details of construction and the arrangement of components set forth in the following description or illustrated in the drawings. The invention is capable of other embodiments and of being practiced or of being carried out in various ways. Also, the phraseology and terminology used herein is for the purpose of description and should not be regarded as limiting. The use of "including," "comprising," or "having," "containing", "involving", and variations thereof herein, is meant to encompass the items listed thereafter and equivalents thereof as well as additional items.

The dual resolution syringe 10 of the present invention is shown in Figs. 1A-1B which illustrate the syringe in two selected positions, the functions of which will be described in detail in connection with the other figures. The syringe 10 comprises a plunger 20, a housing 60 concentric with and movable relative to the plunger, and a piston 40 movable in and relative to the housing. The housing 60 defines a fluid receiving chamber 30 at one end of the housing. As seen by comparing Fig. 1A and 1B, the volume of the chamber 30 is variable, controlled by the relative position of the housing 60 and the piston 40. The piston 40 is sized and shaped to occupy selected volumes of the chamber 30 and has an outer surface 64 of the piston that is at least in part spaced from the inner surface 66 of the housing. The piston 40, thus has an end with a contiguous outer surface 64 spaced from the inner surface 66 of the housing, in part defining the volume of the chamber. The outer surface 64 of the piston is preferably uniformly spaced from the inner surface 66 of the housing to form a portion 70 of the chamber 30. This annular portion 70 thus defines an annular chamber between the outer surface of the piston 64 and the inner surface 66 of the housing. Other shaped segments, however, are contemplated. This may be achieved by shaping the outer surface 64 other than cylindrical. A second portion 72 of the chamber 30 includes the portion between the plunger 20 and the adjacent end of the piston 40. In one embodiment, the maximum volume of the first portion 70 of the chamber 30 is significantly less than the maximum volume of the second portion 72 of the chamber 30. A multiplying factor between the cross-sectional areas of the two portions 70, 72 of approximately 100 is preferred.

The syringe further includes a sealing means 24 which defines an end of the chamber at the end of portion 70. In one embodiment, the sealing means is a compression seal 24 fixed to the inner surface 66 of the housing and is axially movable with the housing relative to the piston 40. In one embodiment, the compression seal 24 is a canted coil spring seal, although other compression seals may be used. Movement of the piston 40 toward the plunger 20 reduces the volume of the chamber 30 by a volume equal to the volume of the piston 40 that moves through the compression seal 24. Conversely, movement of the piston 40 away from the plunger 20 increases the volume of the chamber 30 equal to the volume of the piston moved in the opposite direction through the compression seal 24. In one embodiment, movement of the housing 60 and

sealing means 24 relative to the piston 40 changes the volume of the first portion 70 of the chamber and movement of the piston 40 relative to the plunger 20 changes the volume in the second portion 72 of the chamber.

The volume of the chamber 30 may be varied by movement of the housing 60. From Fig. 1A to 1B, the housing 60 and the piston 40 move down away from the plunger 20 and the volume of the chamber 30 is increased. In one embodiment, the volume of the chamber 30 can be varied by either movement of the housing 60 relative to the plunger 20, movement of the piston 40 relative to the plunger 20, or cooperative movement of both the housing 60 and the piston 40 with respect to the plunger 20.

The syringe further comprises a second sealing means 28 for the chamber 30. This wiper seal 28 is located on the end of the plunger 20 adjacent to the chamber 30. The wiper seal 28 is fixed to the plunger 20 and provides a sealing means between the plunger and the inner surface 66 of the housing and also functions in part as the other defining end of the chamber 30. Located in the middle of the wiper seal 28 is an axial hole 15 providing an exit and entrance for fluid entering the chamber 30 that is contiguous and continuous with an elongated passage 22 extending through the plunger 20. Fluid flows in and out of the chamber 30 through the passage 22. As the volume of the chamber 30 expands and contracts, the fluid in the passage 22 either moves into the chamber 30 or moves out through the passage 22. Additionally, the piston 40 is sized to only move a portion of the fluid in the chamber 30 into the elongated passage 22 extending through the plunger 20. Further, the sealing means 24 and the piston 40 are positioned within the housing 60 to move a portion of the fluid in the chamber 30 into the elongated passage 22 extending through the plunger 20.

In an alternative embodiment, shown in Fig. 2, the wiper seal 28 is cone-shaped with a channel running therethrough to axial hole 15, positioned with the larger end proximate the chamber 30 and the smaller end proximate the plunger 20. This shape helps to catch any rising air bubbles and sweeps the air bubbles that are clinging to the wall inward and upward in the cone-shaped seal through the channel and out of the syringe. Small air bubbles within the chamber can lead to measurement inaccuracy in the chamber. The above described embodiment helps to eliminate this problem.

Figs. 1A-1B show a detailed view of the syringe 10. The housing 60 may comprise a glass annular section 62 and a continuous metal annular section 44. In alternative embodiments, the metal housing may be telescoping, and the exact placement of the glass and the metal may vary. One benefit of the glass section 62 is to maintain optimal visibility of the portion of the piston within the chamber and the wiper seal. It is understood that any type of transparent material, such as glass or plastic, would be beneficial to maintain optimal visibility of the portion of the piston within the chamber.

Attached to the metal section 44 of the housing is a cylindrical tube or bushing 68, preferably made of a low friction plastic of the acetyl family and is fixed to the metal section 44 intermediate the ends of the section, such as by press-fitting it into the metal section. The lower end of the bushing 68 defines a ledge 46 which provides a stop for tab stop 48. Tab stop 48 comprises an annular flange fixed to and extending from the lower end of the piston 40. Tab stop 48 is described at greater length below. A housing seal 26, such as an O-ring may be located between the housing 60 and the bushing 68 to provide a seal between the glass housing 62 and the metal housing 44, or the housing seal 26 may be achieved with epoxy or other bonding material without the use of an O-ring.

The syringe as shown in Figs. 1A and 1B may be used in conjunction with an ancillary system for successive single aspirations and ejections or multiple sequential aspirations and ejections.

In the embodiment of Fig. 5 which shows a typical hookup for a syringe, a tubular member 50, adjacent the plunger 20, is connected to the top outlet of the plunger 20. The tubular member 50 retains fluid selectively in fluid communication with the fluid contained in the chamber 30 and the passage 22 extending through the plunger 20. The chamber 30 volume decreases by fluid moving out of the chamber 50, into the passage 22, and then further into other portions of the tubular member 50, depending on the position of a chamber valve 32, hereafter described. Likewise, the chamber volume increases by fluid in the tubular member entering the passage 22 extending through the plunger and filling the chamber 30.

At the connection between the tubular member 50 and the plunger 20 is a chamber valve 32. The chamber valve 32 controls the direction of fluid flow out of the

passage and the source of fluid into passage 22. The chamber valve 32 defines a storage container 34 side and a probe 36 side of the tubular member 50. The operation of this valve 32 is best illustrated in Figs. 6.1-6.5 and Fig. 11 which also illustrate the basic aspiration process described in greater detail below. In Fig. 5, the chamber valve 32 is illustrated in position for fluid communication between the syringe 10 and the probe 36 side. This position is primarily for aspiration and transferring of samples. Other figures, such as Fig. 11.4 show the chamber valve 32 positioned for fluid communication between the syringe 10 and the storage container 34 side. This position is for initially priming the syringe and for increasing the volume of fluid in the chamber 30, hereafter described in detail. When priming the syringe, the tubular member 50 is filled with the fluid continuous with the fluid in the storage container 34. Additionally, the priming step may include moving a portion of the fluid in the tubular member into the chamber 30.

The piston 40 is moved within the housing 60 by forces generated by a resilient upward urging means, such as a helical spring 42, working within the boundaries set by the housing cap 122 and the bushing ledge 46 as shown in Fig. 1A and 1B. In one embodiment, the piston 40 defines an elongated internal space 58 within which a portion of the spring 42 extends and engages the upper end of the internal space 58. The elongated space 58 extends from one end of the piston to a point short of the other end of the piston. The helical spring 42 is positioned to extend into the elongated space with one end of the spring engaging and bearing against the end of the elongated space 58 within the piston, while the other end of the spring engages a housing cap 122 which is secured at the end of the housing remote from the plunger 22. The housing cap 122 is secured to the metal section 44 of the housing. The movement of the piston 40 into the chamber is limited by the tab stop 48 located on the piston or by the fixed plunger wiper seal 28. As the piston moves towards the plunger, the tab stop 48 prevents further movement of the piston as it contacts the ledge 46 on the bushing 68. The spring may always be loaded to keep the piston in position by itself. Other means for moving the piston can also be used, such as by pressurized air or fluid, by gravity, or by other types of linear actuators.

In one embodiment, the syringe is used for selectively dispensing from a chamber, a first and second volume of fluid having different volumes respectively, in the order of magnitude of at least 3 to 1. The syringe includes a housing which defines at least in part the chamber, and a piston positioned within the housing, defining a volume less than the volume of a coextensive length of the chamber.

In the embodiment of Figs. 1A-1B, the housing cap 122 has a tap 120 which is fitted for connection to a motor or actuator (not shown) and is removably attached to the housing 60. In one embodiment, the movement of the housing 60 is automated. The housing 60 may be moved by any form of a motor or actuator. While the housing cap 122 is removably attached to the tap 120 by the use of a threaded connection, any form of connection, permanent or removable would be included in the scope of the invention. The housing cap 122 closing the end of the housing remote from the plunger, further includes a housing cap post 124 fixed to the housing cap which keeps the spring 42 axially aligned. The housing cap post 124 extending coaxially with the helical spring provides lateral stability to the spring 42 as it compresses and expands.

The syringe of this invention provides aspiration shown in Figs. 6.1-6.5 and ejection or dispensing, shown in Fig. 7.1-7.5 of fluids in two resolutions. Bulk Mode is defined as a coarse (low) resolution/high flow/high volume mode of the dual resolution syringe. In the Bulk Mode, the housing and the piston move together, causing the volume in the chamber to change. In Bulk Mode, the volume is displaced due to a change in the volume of the second portion 72 of the chamber. The volume displaced is equal to the cross-sectional area of the housing multiplied by the vertical displacement of the piston. If the housing is cylindrical and the radius of the inner surface of the housing is "R1" and the vertical displacement of the housing and the piston is "X", then the volume displaced is equal to $\pi(R1)^2 X$. This is how volume displacement in a conventional single piston positive displacement syringe is calculated.

Differential Mode is defined as a fine (high) resolution/low flow/low volume mode of the Dual resolution syringe. In the Differential Mode either the housing moves relative to the piston, or the piston moves relative to the housing. In Differential Mode one of either the piston or the housing is stationary. As previously stated, the outer surface 64 of the piston is preferably uniformly spaced from the inner surface 66 of the

housing to form a first portion 70 of the chamber 30. In Differential Mode, the volume displaced is equal to the volume change in the first portion 70 of the chamber. This volume change is equal to the difference in the cross sectional area of the housing and the piston multiplied by the vertical displacement of either the piston or housing relative to one another. If the piston is cylindrical and the radius of the piston is "R2", then the displaced volume is equal to $[\pi(R1)^2 - \pi(R2)^2]X$.

Bulk and Differential Mode provide many advantages in the present invention. For example, when in Bulk Mode, the syringe is capable of metering a large volume of fluid very quickly and within a high flow rate. Then, in Differential Mode, the syringe is capable of metering a very precise and accurate small volume of fluid very smoothly. Since the syringe is capable of switching back and forth between Bulk Mode and Differential Mode, a wide range of precision and flow rate/volume is obtained with the syringe of the present invention. Alternatively, Bulk and Differential Mode may be used to provide an aspiration resolution that differs from the dispensing resolution.

Fig. 6.1 represents a "home" or top position, at the start of the Differential Mode. The top of the piston 40 is in contact with the wiper seal 28 and the spring is fully compressed. Previous to this position, the device had been primed by movement of the chamber valve 32 to permit fluid communication between the storage container 34 side and the syringe 10. Fig. 6.2 illustrates downward movement of the housing 60 relative to the piston 40. This operates the differential capabilities of the present invention, as the volume aspirated into the device is equal to the difference in cross-sectional areas between the piston and the housing times the distance or height traveled. This Differential Mode enables high precision and accuracy. Fig. 6.3 shows the transition point between Differential Mode and Bulk Mode, because the ledge 46 on the bushing contacts the tab stop 48 on the piston. At this stage, the spring 42 is minimally compressed. As the housing 60 continues to move in the downward direction, Fig. 6.4 shows a midpoint in Bulk Mode. The piston 40 and the housing 60 move together causing the volume of the chamber 30 to increase in the second portion 72 of the chamber. In Bulk Mode, the volume aspirated is relatively large and the device operates similar to a standard single piston syringe. Fig. 6.5 illustrates a maximum chamber 30 volume.

Fig. 7.1 shows the device at a bottom position, similar to Fig. 6.5. In Fig. 7.2 the housing moves up in Bulk Mode, causing movement of the compression seal 24 against the inner surface 66 of the housing, displacing a volume of the second portion of the chamber. Fig. 7.3 shows the transition point between Differential Mode and Bulk Mode where the piston 40 contacts the wiper seal 28 while Fig. 7.4 illustrates a midpoint in Differential Mode. By Fig. 7.4, the fluid in the chamber 30 has generally traveled through the elongated passage 22 and is approaching the probe tip 38 for dispensing. Fig. 7.5 shows the device back to the "home" or top position, with the system primed and ready for dispensing.

The combination of Bulk Mode and Differential Mode in the syringe of the present invention enables this device to accurately and precisely pick up a minute sample (in Differential Mode) and then blow it off touchlessly with a high velocity (Bulk Mode) via a sufficiently large safe air buffer zone to provide touchless transfer, as shown and later described in Fig. 8C. This entire process of accurately picking up a minute sample and completely transferring it is shown in Fig. 11.

Fig. 8A shows the limitations of the prior art conventional single piston syringes. A tip velocity greater than 1 meter/second should prevent a "hanging drop" on the probe tip for most samples. Larger diameter syringes, such as a 1 milliliter syringe with a 0.181" inside diameter can impart enough flow rate to a sample to give a tip velocity over 1 meter/second using a probe tip with a diameter as large as 0.020". The resolution for a syringe of this size is 0.06 mm/microliter or 424 microliters/inch. This equates to a maximum flow of 424 microliter/second, using a fast automated instrument speed of 1"/second. With a traditional whole step stepper motor drive with 2000 steps over a full syringe length of 6 cm (2.37"), the resolution converts into 0.5 microliter/step (500 nanoliters/step). It is generally accepted, and also described in further detail below, that with a 1000 microliter volume syringe, the smallest volume sample one can aspirate and still achieve consistent precision and accuracy better than 1% is 100 microliter. If a smaller sample volume is needed with the same precision and accuracy, then a conventional single piston syringe with a smaller inside diameter is used. However, as shown in Fig. 8A, while the resolution of a syringe is higher with a smaller

volume/smaller diameter syringe, the occurrence for a hanging drop increases using a smaller sized syringe, because a sufficient tip escape velocity cannot be reached.

For example, if one needed to accurately pick up a 1 microliter sample with a conventional syringe, Fig. 8A shows that the syringe would need to be as small as 10-100 microliters, and that for such a syringe to impart a tip escape velocity of greater than 1 meter/second to that sample, the probe tip would need to be very tiny – approximately 0.002" to 0.005". But Fig. 8B shows that such a necessary tiny diameter probe tip would require that the length of the sample passing through that tip would be 40 to 620 times as much as the diameter, a destructive ratio. Fig. 8B shows that a 0.020" ID probe tip would give a healthy 10:1 ratio for such a 1 microliter sample, and Fig. 8A shows that the 1 milliliter volume syringe size could easily impart the needed tip escape velocity for such a proper sized tip. However, a conventional syringe whose dispensing resolution must equal its aspiration resolution cannot achieve both. The present invention overcomes these problems by allowing the aspiration resolution to differ from the dispensing resolution.

Fig. 8B further illustrates the limitations associated with the prior art, showing ballistic stability ratios for different sized samples in probes of different diameters. The ballistic ratio is the height to diameter ratio. The greater the ratio the greater the excessive surface tension and surface contact which can cause genetic fragment damage or viscosity effects. A ballistic ratio of approximately 1:1 to 10:1 is ideal to minimize the damage to the sample. However with conventional syringes, this ballistic ratio limits the resolution and the touchless blowoff capabilities.

Fig. 8C shows the fundamental blastoff mechanism. Fig. 8C-1 illustrates a side by side comparison of a 50 nanoliter sample #A, and a 500 nanoliter sample #B, aspirated into a 0.012" probe inside diameter and a 0.020" probe respectively. Fig. 8C-2 shows a clean blastoff of both samples despite their small size. This is possible because while both samples are accurately aspirated in Differential Mode, they are dispensed in Bulk Mode. Fig. 8C-3 illustrates how the prior art syringes, such as a conventional 10 microliter syringe, are capable of aspirating the small samples but fail to blastoff the samples due to their feeble flow rates. In 8C-3#C there is schematically illustrated prior art single piston and chamber which is capable of blast off but not capable of accurately

aspirating small samples, while 8C-3#D shows a prior art single piston and chamber having a much higher ballistic stability ratio than 8C-3#C that is capable of aspirating small samples accurately, but not capable of blastoff. Fig. 8C-3#E, illustrates how the prior art would dispense using Fig. 8C-3#D.

In addition to the aspirating diversity, dual resolution makes the syringe capable of the dilution of small samples with large volumes of diluent using only one syringe. The present invention enables dilution to occur using an internal source for the reagent as shown in Fig. 9.1-9.6. In this particular embodiment, a 0.1 microliter sample is diluted with a 300 microliter diluent in a syringe with a 0.012" ID probe tip. This provides a 3000:1 dilution ratio. In this particular embodiment, the syringe has capabilities of holding 3.5 microliters in the first portion 70 of the chamber, and 300 microliters in the second portion 72 of the chamber. In Fig. 9.1, the syringe starts out in home position with the probe primed all the way to the tip 38. Fig. 9.2 illustrates the aspiration of 3 microliters of air. In this embodiment, a stepper motor (not shown) driving the system moves 600 steps to aspirate this quantity in Differential Mode. In Fig. 9.3 the sample is brought to the probe tip 38 and aspirated in Differential Mode by movement the stepper motor. Fig. 9.4 shows the valve changing to the storage container 34 side and then the syringe 10 moves down in Bulk Mode to increase the volume of the chamber 30. To eliminate backlash, the housing then moves up a small amount. Then the chamber valve 32changes back to the probe 36 side. Fig. 9.6 shows the dispensing of the 0.1 microliter sample along with 300 microliters of the diluent, which in this example is the internal priming fluid. To dispense the fluid, the syringe 10 moves in Bulk Mode. The tiny sample that was accurately aspirated is ejected from the syringe with a controlled amount of an internal reagent. This may be done at a very high velocity to achieve even mixing.

The invention also enables dilution using an external source for the reagent as illustrated in Fig. 10.1-10.8. A tiny sample 200 is aspirated in Differential Mode and a larger dilution fluid 201 is aspirated in Bulk Mode. Both the sample and the diluent are then ejected from the syringe for mixing in container 203. Most conventional syringes are not capable of diluting a small sample using one syringe because the syringe is not capable of accurately metering such a wide range of volumes of fluid. However, Bulk Mode in conjunction with Differential Mode makes dilution with one syringe possible.

Typically, the volumetric difference between Bulk Mode and Differential Mode is at least 3:1.

Figs. 10.1 to 10.8 shows a syringe similar to the one in Fig. 9 where the syringe has capabilities of holding 3.5 microliter in the first portion 70 of the chamber 30, and 300 microliter in the second portion 72 of the chamber. In Fig. 10.1 the syringe is shown completely primed with the storage container solution 204. In Fig. 10.2, 10 microliters of air is aspirated by movement of the housing 60 and in Fig. 10.3, a 300 microliter external reagent or diluent 201 is aspirated in through the probe tip 38. In Fig. 10.4, the chamber valve 32 changes and the housing 60 moves up to empty some of the priming fluid in the chamber 30 to the storage container 34 side. Another volume of air 206 is aspirated in Fig. 10.5, and in Fig. 10.6, a 100 nanoliters sample 200 is aspirated. This second volume of air separates the diluent 201 from the fluid sample 200. In preparation for dispensing the diluent and the sample, Fig. 10.7 shows the syringe repositioning back to Bulk Mode by movement of the chamber valve 32 to the storage container 34 side and movement of the housing 60 all the way down filling the chamber 30. Once repositioned, Fig. 10.8 shows the valve switching back to the probe 36 side to dispense the approximately 308 microliters, comprising the 100 nanoliters sample, the 3 microliters volume of air, the 300 microliters diluent, and approximately half of the first volume of air. Dispensing a portion of the air volume between the diluent 201 and the priming fluid 204 assures that the full amount of the diluent is dispensed, without the risk of intermixing with the priming fluid.

The above dilution examples show how a minute fluid sample and a large fluid volume can be aspirated into the syringe of the present invention with precision and accuracy. Traditional syringes are capable of achieving approximately 1% precision and accuracy. The precision and accuracy of an aspiration is determined by the volume aspirated in comparison to the total volume capable of being aspirated. For example, with a conventional single piston syringe a 10 microliter volume syringe is capable of achieving 1% precision and accuracy aspirating a 0.1 microliter (10 nanoliters) sample. Furthermore, a conventional 1 milliliter volume syringe is only capable of achieving 1% precision and accuracy with a sample as small as 0.01 milliliters (1 microliter). However, the present invention enables a broader range of sample volumes to be

aspirated with precision and accuracy of at least 1%. In a conventional single piston syringe, the maximum volume ratio one can achieve with at least 1% precision and accuracy is 100:1. However, because the present invention implements two modes, a volume ratio greater than 100:1 and even greater than 3000:1 may be achieved with the same precision and accuracy.

In one embodiment, the present invention consists of a device that can provide fluid aspiration as fine as that of a 10 microliters volume syringe (4.24 microliters /inch, inside diameter of 0.01814") while at the same time, when driven at a speed of 1 inch per second, can provide flow as fast as a 1 milliliter volume syringe (424 microliters /inch, inside diameter of 0.01814") to deliver a sample through even a large 0.20" ID tube (#21 gage hypodermic needle) at a velocity of 1.8 meters per second.

In a further method of operation of the syringe 10 shown in Fig. 11, a tiny or minute quantity of a fluid sample is transferred. Tiny is defined as a small quantity in the order of magnitude of 1 microliters – 100 nanoliters. Minute is defined as a small quantity in the order of magnitude of 10-100 nanoliters. The tubular member 50 is usually primed with a first fluid 220, which involves filling a portion of the tubular member 50 with the first fluid as shown in Fig. 11.1. The tubular member is primed with the fluid 220 from the storage container 34 to flush out any air or fluid from the tubular member and chamber 30. The priming step also includes filling the chamber 30 and the passage 22 extending through the plunger with the first fluid 220. Then in preparation for the aspiration of the sample, a portion of the tubular member near the first end or probe tip 38 of the tubular member is devoid of the first fluid 220. In the embodiment of Fig. 11.2, this is accomplished by aspirating a quantity of air 221. This amount of air is defined as an air gap or air buffer zone which facilitates the touchless transfer of the minute sample. Then, the probe tip 38 is introduced into a reservoir 224 of the sample 225, as shown in Fig. 11.3. Fig. 11.4 illustrates that once the sample 225 is aspirated, the chamber valve 32 changes to provide fluid communication between the syringe 10 and the storage container 34 side. In preparation for ejecting the sample, with the syringe 10 open to the storage container 34 side, the housing 60 moves farther down, repositioning to the Bulk Mode zone and increases the volume of the chamber 30 with fluid from the storage container 34 side. Differential Mode may provide enough precision and

accuracy for larger volumes in which the error from the hanging drop may be small, but to blowout a tiny sample accurately without the significant (and often variable) error of a hanging drop, Bulk Mode may be needed to provide the necessary ejection or air blowout velocity. By first switching the chamber valve 32, the syringe is repositioned to Bulk Mode without disturbing the aspirated sample on the probe 36 side. When the repositioning is completed, as shown in Fig. 11.5, the chamber valve 32 switches back to provide fluid communication between the syringe 10 and the probe 36 side. The exact position in the Bulk Mode zone does not matter as long as it starts at a position that gives enough room to let the syringe blowout the sample and the desired volume of air out and off of the probe tip 38, while still remaining in the Bulk Mode zone.

The fluid sample 225 is ejected from the first end 227 of the tubular member by movement of the first fluid 220 from the tubular member. This forces a quantity of air positioned between the first fluid and the fluid sample from the tubular member, entraining the fluid sample 225, and positively moves it from the first end 227 by the force of air movement as shown in Fig. 11.6. The volume of air 221 ejected is significantly larger than the minute sample 225. The volume of air along with the probe tip 38 diameter permit the minute sample 225 to be ejected intact from the probe tip 38 with the necessary high flow rate of Bulk Mode. The quantity of air 221 positioned between the priming fluid 220 and the fluid 225 sample imparts an air blowout velocity greater than 1 meter per second.

Experimentation has shown that if the sample volume picked up was 1 microliter with an 0.020" inside diameter probe, then the desired total air blow out volume may be 7 or 8 microliters out of a total 10-15 microliters of air aspirated. If the sample volume picked up was 0.1 microliters (100 nanoliters) or less with, for example a 0.012" ID probe then the total air blow out volume may be 2 microliters out of a total of 3-5 microliters of air aspirated. Preferably, the volume of the first fluid aspirated is in the order of magnitude of 10 times the second volume of fluid. However, the first volume of fluid may be in the order of magnitude of 100 times the second volume of fluid or even greater.

In a further method of the present invention, a fluid sample in the order of magnitude of about 1 microliter or less is delivered by placing the sample in a tubular

member having an open end and an inner diameter of in the order of 0.020" or less, and thereafter impelling the sample through the open end under the influence of a fluid medium moving through the tubular member at a speed in excess of about one meter per second.

A further embodiment of the invention shown in Fig. 12 enables the aspiration of a sample and subsequent sequential touchless ejections of multiple smaller discrete portions of the sample. As previously described and shown in Fig. 12.1 -12.2, first the tubular member 50 is primed and a volume of air 221 is aspirated up into the probe tip 38. The fluid sample is then brought into contact with the probe tip 38 to aspirate the desired volume of the sample 225 as shown in Fig. 12.3. In one embodiment, the volume of the fluid sample aspirated is much larger than the volume of the individual sample volume aliquots or portions that will be discretely ejected. For example, if a preferred individual sample volume is 500 nanoliters, then the total sample volume aspirated might be 10 times that amount.

A second volume of air 221A is then aspirated through an air shunt 52 shown in Fig. 12.4. The air shunt 52 is an extension of the probe 36 body that branches off ending in an air shunt valve 54 which may be a valve position shared with the chamber valve 32. The air shunt 52 extends from the tubular member in fluid communication with the air shunt valve 54. When the air shunt valve 54 is opened, air enters the air shunt 52, bisecting the aspirated fluid sample 225 into two distinct volumes. The air shunt 52 is positioned so that the volume of the fluid sample between the entrance of the air shunt into the probe body and the probe tip 38 after the bisection is equal to the desired individual sample aliquot volume. Therefore the individual sample volume, or separated aliquot 225A, is separated from the remaining fluid sample in the tubular member 50 by the volume of air 221A aspirated through the air shunt valve 54. Once the individual sample volume of the desired amount is positioned at the probe tip 38, the air shunt valve 54 is closed.

In preparation for ejecting the individual sample, the chamber valve 32 is switched from the storage container 34 side to the probe 36 side and the syringe is positioned to Bulk Mode for ejecting the sample as shown in Fig. 12.5. Since the chamber valve 32 was switched to provide fluid communication between the syringe 10

and the storage container 34 side, the priming fluid entering the chamber 30 comes from the storage container 34. The chamber valve 32 switches back to open up to the probe 36 side opening up the passage 22 leading into the chamber 30 to the probe 36 side. Remaining in Bulk Mode, the housing 60 moves up towards the plunger 20 to eject the individual sample volume 225A out of the tubular member 50 at a high velocity by movement of the priming fluid toward the probe tip 38 shown in Fig. 12.6. In one embodiment, the housing 60 moves up a distance calculated to dispense a volume of air equal to approximately 50-80% of the volume of air 221A bisecting the fluid sample 225 volume. For example, if 5 milliliters of air is aspirated through the air shunt valve 54, the housing 60 moves up towards the plunger 20, a distance calculated for the ejection of about 3 milliliters out of the probe tip 38. This volume ejected from the tubular member 50 does not have to be precise. The volume of air selected is intended to provide a non-precise ejection by the coarse Bulk Mode to extend safely into the main body of the air buffer zone, while also expelling the much smaller sample aliquot 225A at the tip 38. This will completely blastoff the individual sample aliquot from the tip 38 while still maintaining a separation between the remaining fluid sample in the tubular member 50 and the priming fluid in the tubular member.

To set the system up for the next individual sample volume ejection, the remaining fluid sample in the tubular member 50 must be repositioned as shown in Fig. 12.7, to measure out the desired volume of the next individual sample volume aliquot. In one embodiment, the fluid sample is repositioned with an air detector 56 located on the tubular member 50, located approximately where the air shunt 52 branches out from the probe 36. A conventional air detection system may be used, depending on the specific applications involved. One embodiment of the present invention employs an optical detector that senses the change between air and a fluid. However, other detection systems may be used. Using a detector, the fluid sample in the tubular member 50 is moved toward the first end or probe tip 38 until the fluid sample is adjacent the air shunt 52 as shown in Fig. 12.8. Then, the remaining fluid sample is further moved toward the first end until the fluid sample is adjacent the first end or probe tip 36 as shown in Fig. 12.9.

The Differential Mode of the dual resolution syringe is used to precisely accomplish the repositioning of the fluid sample flush with the probe tip 38. First the

chamber valve switches to the storage container side and the housing 60 and the compression seal 24 move up with respect to the plunger 20, reaching the bottom of the Differential Mode. The housing then moves slowly up in the Differential Mode, slowly and smoothly pushing the remaining sample downward. In one embodiment, as soon as the air detector 56 detects the leading edge of the fluid sample the pump motor stops, thus stopping the movement of the housing 60 and the compression seal 24 as shown in Fig. 12.8. Conventional circuitry may be used to control the pump operation in response to the air detector. In this step, it may be beneficial for the housing and the compression seal to move slowly, smoothly and precisely to prevent any of the fluid sample in the tubular member from seeping past or overshooting the air detector 56. This accurate movement of the dual resolution syringe could not be accomplished adequately in Bulk Mode, or with any large single piston syringe. A microprocessor controls how far the chamber must move to fill the volume between the air detector 56 and the probe tip 38, and communicates with the motor to move the additional distance. This pushes the fluid sample in the tubular member 50 down until it is again flush with the probe tip 38 as in Fig. 12.9. Next, another individual sample volume aliquot or sample portion is separated from the remaining portion of the fluid sample in the tubular member 50 by bisecting it with a third quantity of air and then the sample is ejected from the probe tip 38 as explained above. These steps are repeated until the desired number of separate aliquots of sample have been dispensed.

In an alternative embodiment, the fluid sample in the tubular member is repositioned down to the first end or probe tip 38 in one step rather than in two steps. In the one step process, an air detector 56 is not required, but rather the fluid sample is moved down the tubular member 50 by a distance that would approximately bring a portion of the sample to the level of the probe tip 38. However, the two step process may be preferred because then the exact position of the fluid sample in the tubular member is reset to a calibrated position in the first step, and the individual sample volume is measured out precisely and accurately in the second step. Additionally, while in one embodiment, the system is automated with an air detector 56 connected to the pump motor, the scope of the invention encompasses many manual operations and sample positioning detecting schemes as well.

In an alternative embodiment shown in Fig. 3, a piston 140 is tapered slightly with an outer diameter that decreases or increases over the length of the piston. It is substituted for piston 40 in the other embodiments herein described. This adds flexibility to the syringe because one can alter the resolution in the Differential Mode. For example, a syringe of the present invention will have certain resolution capabilities with a piston that has an outer diameter of 0.1810 inches. If the inner diameter of the housing is constant, and the same syringe is used with a piston that has an outer diameter of 0.1806 inches, the resolution capabilities will change because the distance between the inner surface 66 of the housing and the outer surface 64 of the piston increased by 0.004 inches. With a tapered piston design, one can vary the resolution capabilities of the Differential Mode without needing multiple pistons. To vary the resolution capability with a tapered piston, the position of the piston is adjusted to the desired level. As long as the taper of the piston from one end to the other is deigned to be small, there is not a need for a different sized seal. In one embodiment, the taper is approximately between 0.001-0.004 inches. The taper could be outside of this range, however too large of a taper will create sealing problems between the outer diameter of the piston and the housing. However, it is understood that this problem is alleviated with using a flexible or compressible seal.

The present invention is designed for use for either reusable syringes or disposable syringes. Typically the reusable market incorporates a glass portion of the housing, while a disposable one-time use syringe employs a plastic portion of the housing and or plastic tips. The present invention is not limited to a particular type of material or construction. Additionally, in the reusable syringe market, experience has shown that over time the seals and piston may wear out from use requiring replacement parts. The scope of this invention covers the replacement parts associated with the present invention. For example, in one embodiment of the above described syringe assembly that includes an elongated housing with continuous sidewalls that define an outlet end, the present invention includes a closure means for movably sealing the outlet end along the inner surface of the sidewall. The closure means selectively defines different volumes within said housing and also defines an opening there through extending to said outlet end. An example of this embodiment would cover a replacement

plunger and in one embodiment, the replacement plunger includes a cone-shaped seal with a channel there through with the larger end of the seal proximate the outlet end. As previously explained, this seal shape helps to catch any rising air bubbles and sweeps the air bubbles that are clinging to the walls inward and upward in the cone-shaped seal through the channel and out of the syringe.

In an alternative embodiment, illustrated in Fig. 13 dual resolution is accomplished with a syringe 110 for selectively dispensing from a chamber 116 a first or second volume of fluid having different volumes in the order of at least 3 to 1. This syringe 110 includes a piston 379 positioned within the housing 360, and the piston includes at least two distinct segments, 112 and 114, the smaller of which may slide in and out of the larger segment via a seal 382. The first or larger segment 112 of the piston moves within the housing 360, varying the volume of the chamber 116. Likewise, the second or smaller segment 114 of the piston 379 moves within the housing, varying the volume of the chamber 116. The first and second segments of the piston 112, 114 can either move independently of one another or together. In one embodiment, the housing is stationary and both the first and second segments 112, 114 move relative the housing. In another embodiment, the housing is movable relative to the piston. The first segment 112 of the piston has a slightly larger cross-sectional area compared to the second segment of the piston. In one embodiment, the multiplying factor between the difference between these two cross-sectional areas and the area of either segment alone is at least 3 and can easily be 100. This difference in cross-sectional areas helps to facilitate the dual resolution capabilities of the syringe. Further if the housing also moves one may create a triple resolution syringe which may provide increased precision. Movement of the first segment of the piston 112 varies the volume of the chamber in the above described Bulk Mode, while movement of the second segment of the piston 114 varies the volume of the chamber in the above described Differential Mode. Fig 13 shows the outer surface of the first segment of the piston separated from to the inner surface of the housing by sealing means 380. The second segment 114 of the piston is encompassed within a recessed portion 362 in the first segment 112 and slides along seal 382 by spring 364. The means for selectively moving the first and second segments of the piston 112, 114 to displace a second and first volume of fluid includes all previously

mentioned means in other embodiments of the present invention. Also, the scope of the invention includes other embodiments where the arrangement of the first and second segments of the piston within the housing is varied. Furthermore, this alternative embodiment may include a notch 370 in a piston segment to provide for fluid communication when the piston segment approach the passage 322. This embodiment may be described as a telescoping piston arrangement, or also a plunger within a piston. The invention also contemplates the use of pistons with more than two segments.

The embodiment of Fig. 14 illustrates a telescoping piston/plunger arrangement similar to Fig. 13 incorporated into a stationary housing. This embodiment is advantageous because it enables dual resolution capabilities using a glass housing and system of a conventional single piston syringe. Segments 114 and 112 move relative to the stationary housing 360. Segment 114 is in a telescoping arrangement, capable of moving inside of segment 112. The volume of the chamber 116 is a function of the position of each segment 112 and 114.

All of the above described embodiments allow a volume of air to be aspirated that is many times greater than the size of one minute sample. This volume of air, along with the probe tip diameter, permits the precise aspiration of a minute sample by the fine resolution Differential Mode of the syringe and its touchless intact ejection from the probe tip by the necessary high flow rate of the Bulk Mode.

In one embodiment, the single piston syringe of the present invention is provided with a dynamically sealed spring-driven piston that operates within a dynamically sealed motor-driven housing. A chamber within the housing is defined by two seals that permit adjustment of the chamber volume by movement of the piston and the housing with respect to an immobile plunger. Two different space-occupying masses, the piston 40 and the housing 60, enable the syringe to accurately and precisely meter minute volumes of fluid while also deploying relatively very large volumes and high powered flow velocities. This range of accuracy and flow capacity provides a unique ability to transfer minute liquid samples without the need to touch them off.

In the alternative embodiment illustrated in Figs. 4A-4C, the syringe 200 only operates in Differential Mode. Figs. 4A and 4B show how the first portion 70 of the chamber remains in fluid communication with the elongated passage extending through

the plunger via a breakout hole 208. From Fig. 4A to Fig. 4B, the housing 60 moving down increases the volume in the chamber portion 70. In this embodiment, there is not a Bulk Mode, but rather the device only operates using differential capabilities. Fig. 4C shows one embodiment where the plunger 20 and the piston 40 are formed into one piece with the wiper seal 28 slid up over the assembly, fixed just above the breakout hole 208.

This embodiment shows how the present invention permits positive displacement fluid handling technology to meter samples in the microliter and nanoliter scale. When the positive displacement element, such as a piston or the plunger, moves toward the outlet, the fluid is pushed outward. When the positive displacement element is withdrawn, it exerts a vacuum and pulls the fluid into the sampling device inward. Positive displacement devices are operated automatically or manually, and in general it is known that they are highly controllable and highly developed, reliable and trusted. Typical syringes operate as a positive displacement device. One example is a syringe having a solid plunger with a typical Teflon tip at the end of the plunger serving as an outwardly-pressing seal when it slides against an inner surface of a tube. Other variations use different sealing materials such as polyethylene, and other rubber compounds, such as Buna, a synthetic rubber made from the polymerization of butadiene and sodium. Another variation of a positive displacement device includes a single piston that passes through a compression seal inside of a tube.

In the embodiment of Fig. 4, the housing forms a chamber defined by the inner surface of the housing 60 and spaced portions of the outer surface of the piston 40. In one embodiment, the cross-sectional shape of the chamber is annular, however other configurations may be used. This embodiment includes means extending from an end of the piston defining a passage for fluid to flow out of the chamber. In one embodiment, shown in Fig. 4C, there are means extending from an end comprising an extension of said piston having an axially extending passage with one end of the passage in fluid communication with the chamber and the other end of the passage extending outwardly of the chamber. Other means defining a passage for fluid flow may be unconnected to the piston. As described in other embodiments above, the embodiment of Fig. 4A-4C may further include sealing means fixed to the inner surface of the housing, movable relative to the piston or plunger, forming an end of the chamber. This embodiment may

also include a second sealing means fixed to the extension of the piston forming an end of the chamber. This embodiment is used for metering small and minute sample volumes and is advantageous over conventional syringe designs because minute sample sizes can be accurately aspirated using larger components. Since the chamber size is defined as the volume in between the piston and the housing, the sizes of the piston, housing, and sealing means are larger relative to a conventional syringe with the same resolution capabilities. Additionally, this embodiment may be modified to include a piston that has a frusto-conic section forming a tapered section and at least one resilient seal between the inner surface of the housing and a portion of the frusto-conic section.

As described above, the market for positive displacement devices, in particular in the medical and biomedical fields, has demanded finer and finer resolution with better precision and accuracy in metering smaller and smaller samples. This has led to positive displacement devices with smaller inner diameters. However, when manufacturing smaller and smaller inner bores, difficulties arise when trying to maintain precision and accuracy throughout the length. This is also challenging with glass for example, where the internal channel is formed over a mandrel. In addition, small inner diameter bores requires small seals. Both tip seals and compression seals are very difficult to manufacture with precision, and due to their size they wear out and consequently leak relatively quickly.

Due to the difficulty in manufacturing rugged seals, an alternative approach is to eliminate the separate seals so that the sealing takes place between the hard material outer surface of the plunger or piston and the inner surface of the bore tubing directly. In the past, ultra precise and often custom-ground glass syringe plungers were made to slide close inside glass tube bores so that glass provided a liquid tight or even air tight seal on glass. Ceramic pistons inside of ceramic bores have also been used successfully. However, this design leads to many limitations on materials of use, tends to be expensive, and the rigid materials are prone to jamming up if any solid gets inside. Therefore, it shows little promise of economical and practical application value.

However, the present invention overcomes all of these difficulties because there is no need for smaller and smaller parts to meter smaller and smaller volumes when using the Differential Mode. To reiterate, a traditional extremely fine resolution 10

microliter syringe (which is the standard 6 cm or 2.37 inches in length) has a tube inner diameter bore of only 0.018 inches. This corresponds to the seal size required, and is about the size of a needle. This may be too small for practical automated applications but can be used in special research applications. The present invention, with its Differential Mode, can give the same fine resolution equivalent to the above described 10 microliter volume syringe by using a housing or tube with an inner diameter of 0.181 inches (4.6mm) in conjunction with a piston that has an outer diameter of 0.180 inches. The relatively large size of the present invention is comparable to a traditional or standard 1 milliliter (1000 microliter) syringe which is 100 times larger in volume than the above mentioned 10 microliter volume syringe. The size of the present invention is much more practical to manufacture and incorporate into an automated system, and it eliminates the sealing problems associated with using tiny seals.

Having thus described several aspects of at least one embodiment of this invention, it is to be appreciated various alterations, modifications, and improvements will readily occur to those skilled in the art. Such alterations, modifications, and improvements are intended to be part of this disclosure, and are intended to be within the spirit and scope of the invention. Accordingly, the foregoing description and drawings are by way of example only, and the scope of the invention is limited by the appended claims and their equivalents.

What is claimed is:

CLAIMS

1. A method of transferring minute quantities of fluid samples comprising:

priming a tubular member with a first fluid whereby a portion of the tubular member is filled with a first fluid and a portion of the tubular member adjacent a first end thereof is devoid of said first fluid;

introducing the first end into a reservoir of fluid sample; and

aspirating a quantity of the fluid sample into the tubular member while maintaining a space between the fluid sample and the first fluid in the tubular member and thereafter ejecting the fluid sample from the tubular member through the first end by movement of the first fluid toward the first end.

2. A method as set forth in claim 1, wherein the fluid sample is ejected from the first end of the tubular member by movement of the first fluid forcing a quantity of air positioned between the first fluid and the fluid sample from the tubular member, wherein the fluid sample is entrained and positively moved from the first end by the force of air movement.

3. A method as set forth in claim 1 comprising:

providing a chamber containing a quantity of said first fluid continuous with the first fluid in the tubular member;

and at least in part providing said aspirating step by moving a portion of the first fluid in said tubular member into the chamber.

4. A method as set forth in claim 3, wherein the fluid sample is ejected from the tubular member by moving a portion of the first fluid in said chamber into the tubular member.

5. A method as set forth in claim 3 comprising:

providing a housing enclosing the chamber;

and at least in part providing said aspirating step by moving the housing.

6. A method as set forth in claim 5 further comprising:

a piston positioned and longitudinally movable in and relative to the housing;

and at least in part providing said aspirating step by moving the housing and the piston.

7. A method as set forth in claim 4 comprising:

providing a housing enclosing the chamber;

and at least in part providing said ejecting step by moving the housing.

8. A method as set forth in claim 4 further comprising:

a piston positioned and longitudinally movable in and relative to the housing;

and at least in part providing said ejecting step by moving the housing and the piston.

9. A method as set forth in claim 1 comprising:

providing a storage container filled with the first fluid continuous with the first fluid in the tubular member;

and at least in part providing said priming step by moving a portion of the first fluid in said storage container into the tubular member.

10. A method as set forth in claim 9 comprising:

providing a chamber connected to the tubular member;

and at least in part providing said priming step by moving a portion of the first fluid in said tubular member into the chamber.

11. A method as set forth in claim 1 comprising:

a chamber valve in the tubular member, the chamber valve defining a storage container side of the tubular member and a probe side of the tubular member; and

providing said ejecting step by moving the chamber valve from the storage container side to the probe side.

12. A method as set forth in claim 11 comprising:

proving said ejecting step by moving the chamber valve from the probe side to the storage container side.

13. A method as set forth in claim 2, wherein the quantity of air positioned between the first fluid and the fluid sample imparts an air blowout velocity greater than 1 meter per second.

14. A syringe for metering and dispensing incrementally different volumes of fluid comprising:

a plunger with an elongated passage extending therethrough;

a housing concentric with and movable relative to the plunger and at least in part defining a fluid receiving chamber at one end of the plunger;

a piston positioned and longitudinally movable in and relative to the housing, the piston shaped and sized to occupy selected volumes of the chamber and having an outer surface at least in part spaced from the inner surface of the housing; and

sealing means forming an end of the chamber remote from the one end of the piston, said means fixed to the inner surface of the housing and movable relative to the piston, whereby movement of the piston toward the plunger initially reduces the volume of the chamber by a first volume equal to the volume of the piston between the sealing means and the plunger, and thereafter a second volume by relative movement of the sealing means and piston.

15. The syringe of claim 14, further comprising a second sealing means for the chamber, said second sealing means fixed to the plunger, positioned between the plunger and the inner surface of the housing, and defining an end of the chamber proximal the plunger.

16. The syringe of claim 15, wherein the second sealing means is cone-shaped with a channel therethrough, positioned with the larger end proximate the chamber and the smaller end proximate the plunger.

17. The syringe of claim 14, wherein the outer diameter of the piston decreases over the length of the piston.

18. The syringe of claim 14, wherein the piston is sized to only move a portion of the fluid in said chamber into the elongated passage extending through the plunger.

19. The syringe of claim 14, wherein the sealing means and piston are positioned within the housing to move a portion of the fluid in said chamber into the elongated passage extending through the plunger.

20. The syringe of claim 18, further comprising a tubular member adjacent to the plunger, wherein a fluid sample is aspirated and/or ejected through a first end of the tubular member.

21. The syringe of claim 20, further comprising a chamber valve at the connection between the tubular member and the plunger, wherein the chamber valve controls the direction of fluid flow out of the elongated passage and the source of fluid into the elongated passage.

22. The syringe of claim 20, further comprising an air shunt extending from the tubular member in communication with an air shunt valve, wherein air entering the air shunt through the air shunt valve flows into the tubular member and bisects the fluid in the tubular member.

23. The syringe of claim 14, further comprising a resilient means for generating forces to move the piston within the housing.

24. The syringe of claim 23, wherein an elongated space is provided within the piston receiving a portion of the resilient means and engaging one end of the resilient means.

25. The syringe of claim 24, further comprising a housing cap defining an end of the housing, wherein the housing cap engages one end of the resilient means.

26. The syringe of claim 25, wherein the resilient means is a helical spring.

27. The syringe of claim 26, further comprising a post extending from the housing cap and coaxially with the helical spring.

28. The syringe of claim 14, further comprising means for moving the housing with respect to the plunger.

29. The syringe of claim 28, wherein the means for moving the housing is automated.

30. The syringe of claim 14, wherein the cross-sectional area of the piston is greater than the cross-sectional area of the passage extending through the plunger.

31. A syringe for metering sequential different volumes of fluid contained in the syringe including:

a housing;

a piston within the housing; and

a plunger extending from the housing;

a chamber formed in the housing between the plunger and a sealing means between the piston and the inner surface of the housing;

the piston having a volume less than the volume of that portion of the chamber that is coextensive with the portion of the piston in the chamber;

means for aspirating a first volume of said fluid by movement of the sealing means relative to the piston, and thereafter a second lesser volume of fluid by further movement of the sealing means relative to the piston; and

means for ejecting the second volume of fluid by movement of the piston relative to the plunger.

32. A syringe as set forth in claim 31 including a cap closing the end of the housing remote from the plunger, said piston having a wall defining an elongated space extending from one end of the piston to a point short of the other end of the piston, and a helical spring positioned in the elongated space with one end engaging the cap.

33. A syringe as set forth in claim 32 including a post extending from the cap and coaxially with the helical spring.

34. A syringe as set forth in claim 31, wherein the first volume of fluid is in the order of magnitude of 10 times the second volume of fluid.

35. A syringe as set forth in claim 31, wherein the first volume of fluid is in the order of magnitude of 100 times the second volume of fluid.

36. A method of transferring multiple minute quantities of fluid samples comprising:

priming a tubular member with a first fluid whereby the tubular member is filled with the first fluid;

aspirating a quantity of air into a first end of the tubular member;

introducing the first end into a reservoir of the fluid sample;

aspirating a quantity of the fluid sample into the first end while maintaining the quantity of air between the fluid sample and the first fluid

aspirating a second quantity of air into the tubular member through an air shunt, separating the fluid sample into two distinct volumes: a sample portion defined as the

volume of the fluid sample adjacent the first end, and a remaining portion of the fluid sample in the tubular member; and

ejecting the sample portion from the tubular member through the first end by movement of the first fluid toward the first end while maintaining a quantity of air between the remaining portion of the fluid sample and the first end.

37. A method as set forth in claim 36, further comprising:

moving the remaining portion of the fluid sample in the tubular member toward the first end until the fluid sample is adjacent the air shunt; and

further moving the remaining fluid sample toward the first end until the fluid sample is adjacent the first end.

38. A method as set forth in claim 37, further comprising:

aspirating a third quantity of air into the tubular member through the air shunt, separating the fluid sample into two further distinct volumes: the sample portion and the remaining portion; and

ejecting the sample portion from the tubular member through the first end by movement of the first fluid toward the first end while maintaining a quantity of air between the remaining portion of the fluid sample and the first end.

39. A syringe having a housing with a chamber formed therein,

a piston having an end and a contiguous outer surface spaced from the inner surface of the housing in part defining the volume of the chamber;

means for moving the piston to vary the volume of the chamber; and

means for varying the volume defined between the outer surface of the piston and inner surface of the chamber.

40. A syringe as set forth in claim 39 wherein the volume defined between the outer surface of the piston and the inner surface of the chamber forms an annular segment of the chamber.

41. A syringe as set forth in claim 39 including a plunger defining in part the chamber and having an elongated passage extending there through into one end opening into the chamber.

42. A syringe as set forth in claim 41, wherein the housing is concentric with the piston and plunger, and axially moveable relative to the piston and plunger.

43. A syringe as set forth in claim 39 wherein the outer surface of the piston extends to a second end of the piston and defines an elongated space;

a spring extending into the space with one end of the spring bearing against the second end of the piston; and

means at the end of the housing remote from the plunger for securing the other end of the spring.

44. A syringe as set forth in claim 39 having a first sealing means along the inner surface of the housing defining one end of the chamber, axially movable with the housing and relative to the piston and plunger, whereby movement of the sealing means relative to the piston varies the volume defined between the outer surface of the piston and the inner surface of the chamber.

45. A syringe as set forth in claim 44 having a second sealing means around the plunger defining the other end of the chamber.

46. A syringe as set forth in claim 39, wherein said piston is tapered from one end to the other.

47. A method of delivering a fluid sample in the order of magnitude of about 1 microliter and less comprising:

placing the sample in a tubular member having an open end and an inner diameter of in the order of 0.020" or less, and thereafter impelling the sample through the

open end under the influence of a fluid medium moving through the tubular member at a speed in excess of about one meter per second.

48. A syringe for selectively dispensing from a chamber a first or second volume of fluid having different volumes respectively, in the order of at least 3 to 1 comprising:

a housing defining at least in part the chamber;

a piston positioned in the housing and defining a volume less than the volume of a coextensive length of the chamber; and

means for selectively moving the piston with the housing or moving the piston relative to the housing respectively, for displacing said second or first volume of fluid.

49. A syringe for selectively dispensing from a chamber a first or second volume of fluid having different volumes respectively, in the order of at least 3 to 1 comprising:

a housing defining at least in part the chamber;

a piston positioned in the housing, wherein the piston includes at least two distinct segments; and

means for selectively moving a first segment of the piston relative to the housing or moving a second segment of the piston relative to the housing respectively, for displacing said second or first volume of fluid.

50. A syringe having a chamber formed therein including,

a housing;

a piston longitudinally movable within the housing;

a first portion of the chamber defined as the volume between the outer surface of the piston and the inner surface of the housing;

a second portion of the chamber defined as the remaining volume of the chamber, contiguous with the first portion of the chamber including the volume of the chamber not occupied by the piston;

means for moving the piston to vary the volume of the second portion of the chamber; and

means for varying the volume in the first portion of the chamber.

51. A syringe as set forth in claim 50, wherein the multiplying factor between the cross-sectional area of the first portion of the chamber and the second portion of the chamber is at least 100.

52. A syringe as set forth in claim 50 for metering a volume of fluid, having a ballistic ratio between 1:1 and 10:1, wherein the ballistic ratio is the height of the fluid in the syringe to the diameter of the fluid in the syringe.

53. In a syringe assembly, having an elongated housing with continuous sidewalls defining an outlet end,

a closure means for movably sealing the outlet end along the inner surface of said sidewall to selectively define different volumes within said housing, said closure means also defining an opening therethrough extending to said outlet end.

54. The syringe assembly of claim 53, further comprising a cone-shaped seal with a channel therethrough with the larger end of the cone-shaped seal proximate the outlet end.

55. A syringe comprising:

a housing with a chamber formed therein;

a piston extending lengthwise within the chamber and movable relative thereto, the chamber defined by the inner surface of the housing and spaced portions of the outer surface of the piston; and

means extending from an end of the piston defining a passage for fluid outwardly of the chamber.

56. A syringe as set forth in claim 55, wherein said means extending from an end comprises an extension of said piston having an axially extending passage with one end of the passage in fluid communication with the chamber and the other end of the passage extending outwardly of the chamber.

57. A syringe as set forth in claim 56, wherein said piston has a frusto-conic section forming a tapered section and at least one resilient seal between the inner surface and a portion of the frusto-conic section.

58. The syringe as set forth in claim 56, further comprising a sealing means fixed to the inner surface of the housing and movable relative to the piston, forming an end of the chamber.

59. The syringe as set forth in claim 58, further comprising a second sealing means fixed to the extension of the piston having an axially extending passage, forming an end of the chamber.

60. A method of diluting a minute fluid sample with an external reagent comprising:

priming a tubular member with a first fluid whereby a portion of the tubular member is filled with the first fluid;

introducing a first end of the tubular member into reservoirs of a fluid sample and an external reagent;

aspirating a quantity of the fluid sample, wherein the fluid sample is aspirated with precision and accuracy of at least 1% and a quantity of the external reagent into the tubular member, wherein the external reagent is aspirated with precision and accuracy of at least 1%;

ejecting the external reagent and the fluid sample through the first end of the tubular member, wherein the fluid sample is diluted with the external reagent; and

wherein the ratio of the volume of the external reagent to the volume of the minute fluid sample is greater than 100:1.

61. A method as set forth in claim 60, further comprising:

aspirating a quantity of air into the tubular member after the aspiration of the fluid sample and before aspirating the reagent.

62. A method as set forth in claim 60, further comprising:

aspirating a quantity of air into the tubular member after the aspiration of the reagent and before aspirating the fluid sample.

63. A method as set forth in claim 60 comprising:

providing a chamber containing a quantity of said first fluid continuous with the first fluid in the tubular member, a housing enclosing the chamber, and a piston positioned and longitudinally movable in and relative to the housing; and

wherein the fluid sample is aspirated by movement of the housing relative to the piston.

64. A method as set forth in claim 63, wherein the external reagent is aspirated by movement of the housing and the piston.

65. A method of metering fluid samples from a syringe system comprising:

providing a first portion of a chamber and a second portion of chamber;

metering a quantity of a first fluid sample into the syringe system, wherein the first fluid sample is aspirated with precision and accuracy of at least 1%;

metering a quantity of a second fluid sample into the syringe system, wherein the second fluid sample is aspirated with precision and accuracy of at least 1%;

wherein the ratio of the volume of the first fluid sample to the volume of the second fluid sample is greater than 100:1; and

wherein at least in part, the metering step of the first fluid sample is provided by a change in the volume of the second portion of the chamber, and the metering step of the second fluid sample is provided by a change in the volume of the first portion of the chamber.

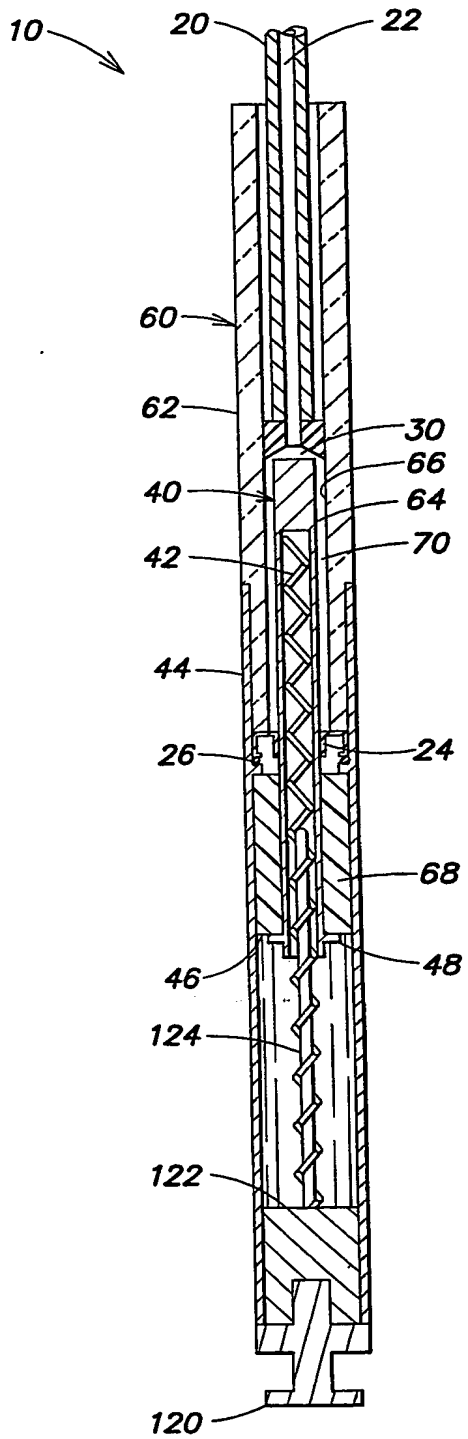
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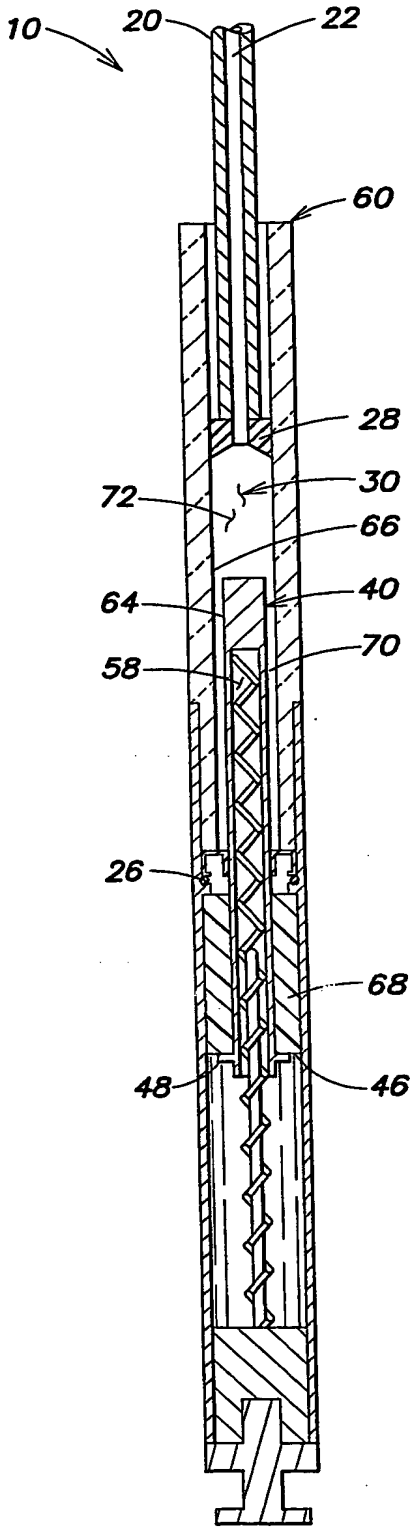
FIG. 1A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46

FIG. 1B

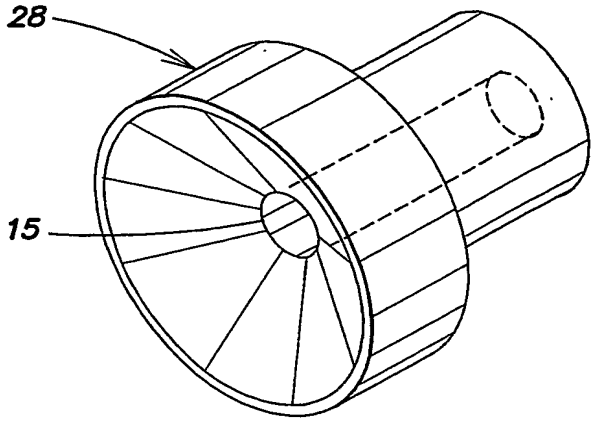

FIG. 2

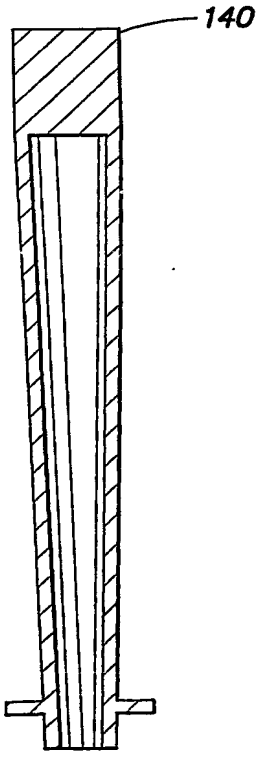

FIG. 3

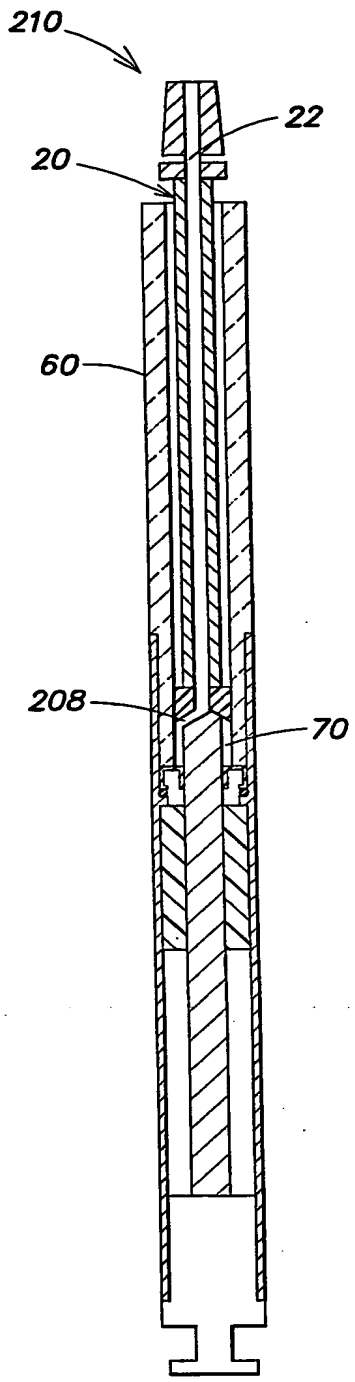

FIG. 4A

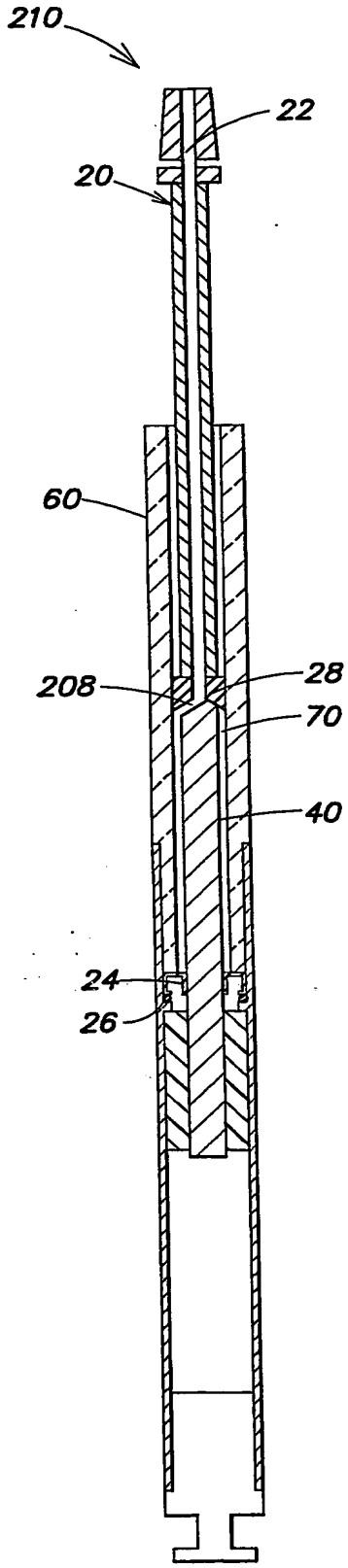

FIG. 4B

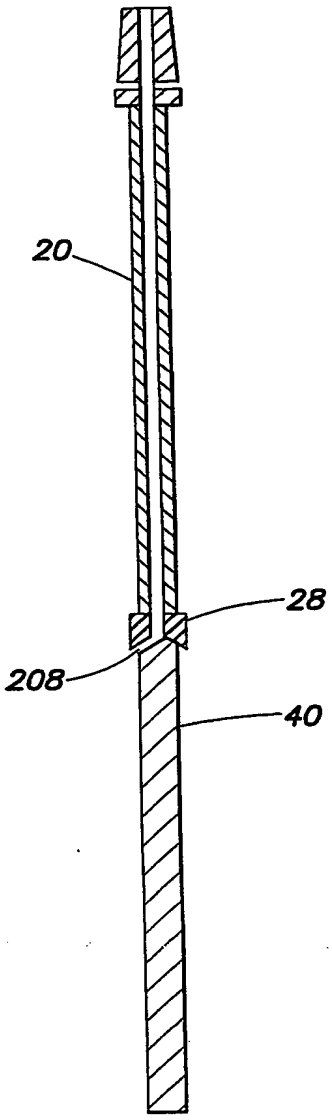

FIG. 4C

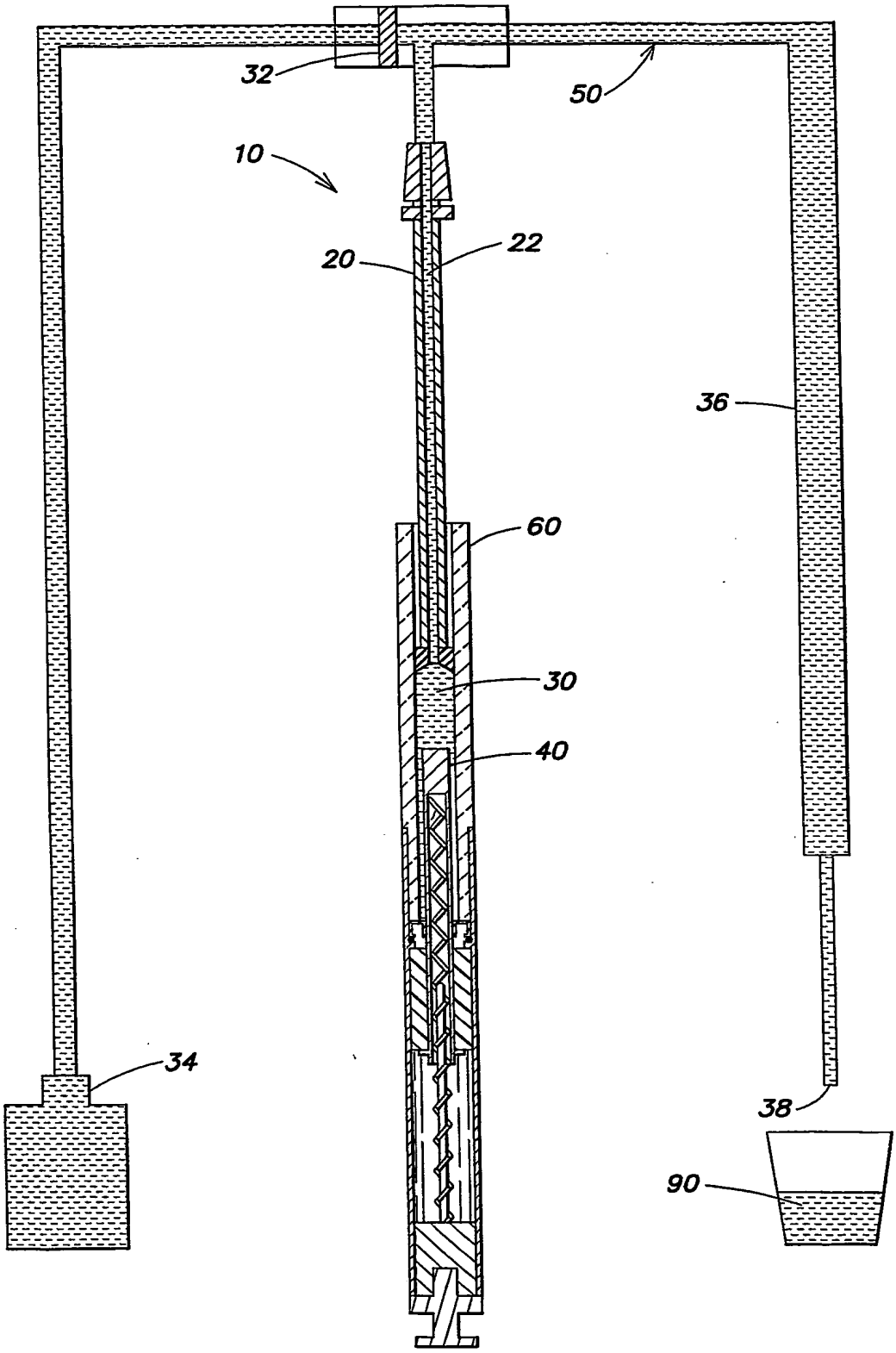

FIG. 5

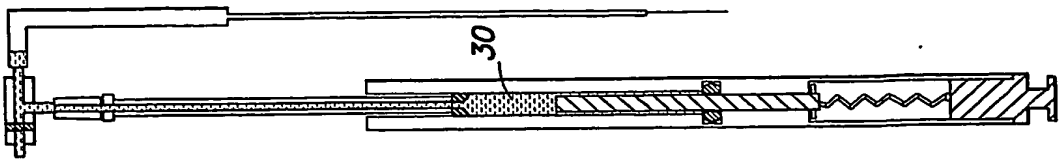

FIG. 6.5

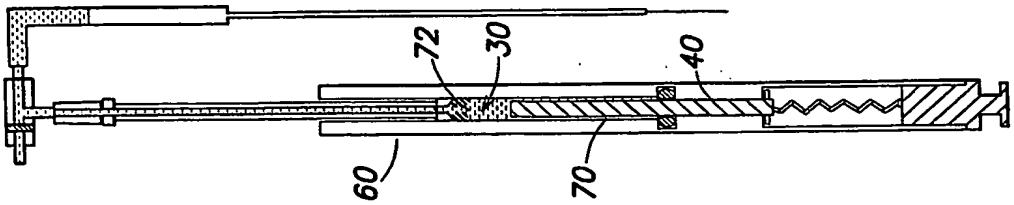

FIG. 6.4

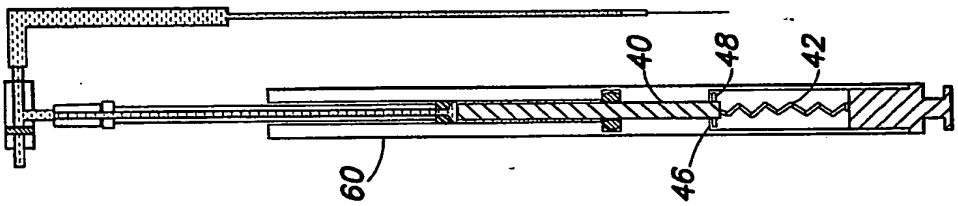

FIG. 6.3

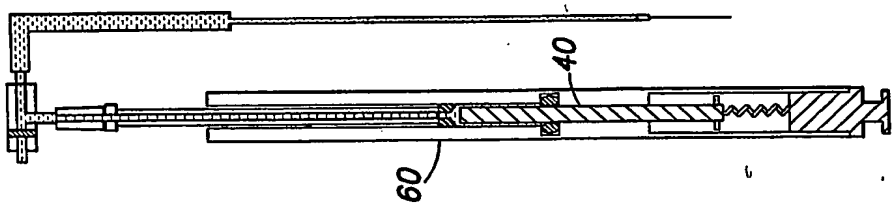

FIG. 6.2

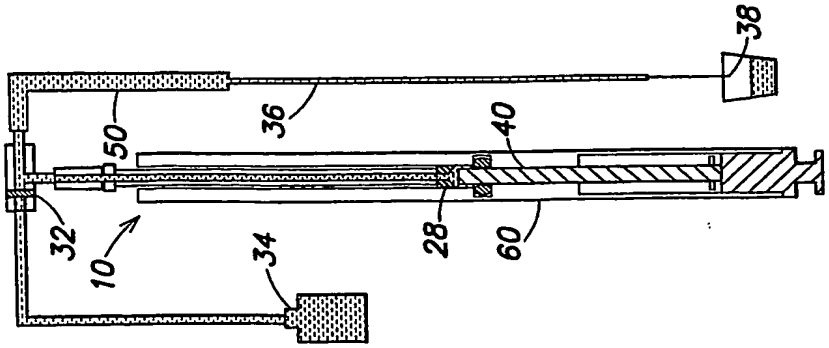

FIG. 6.1

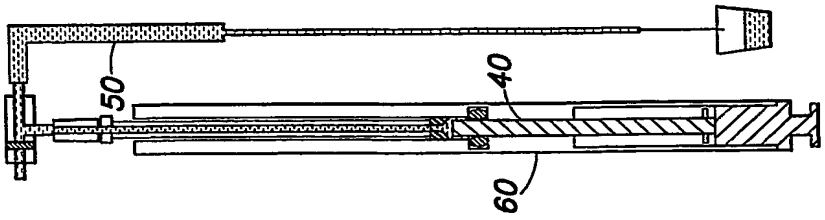

FIG. 7.5

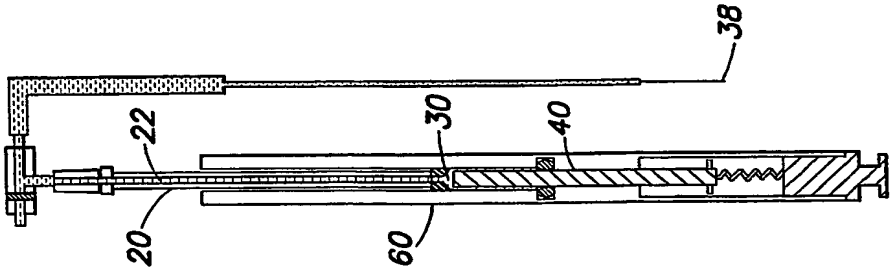

FIG. 7.4

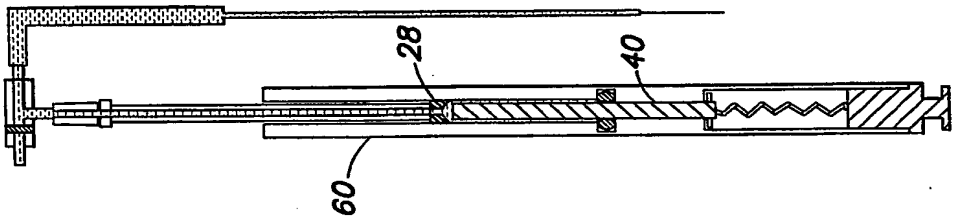

FIG. 7.3

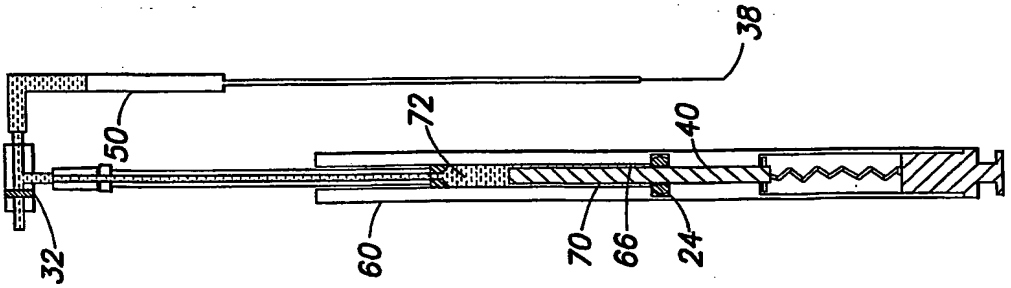

FIG. 7.2

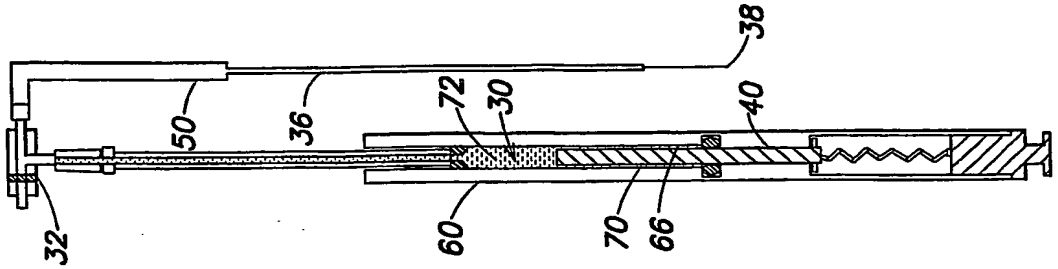

FIG. 7.1

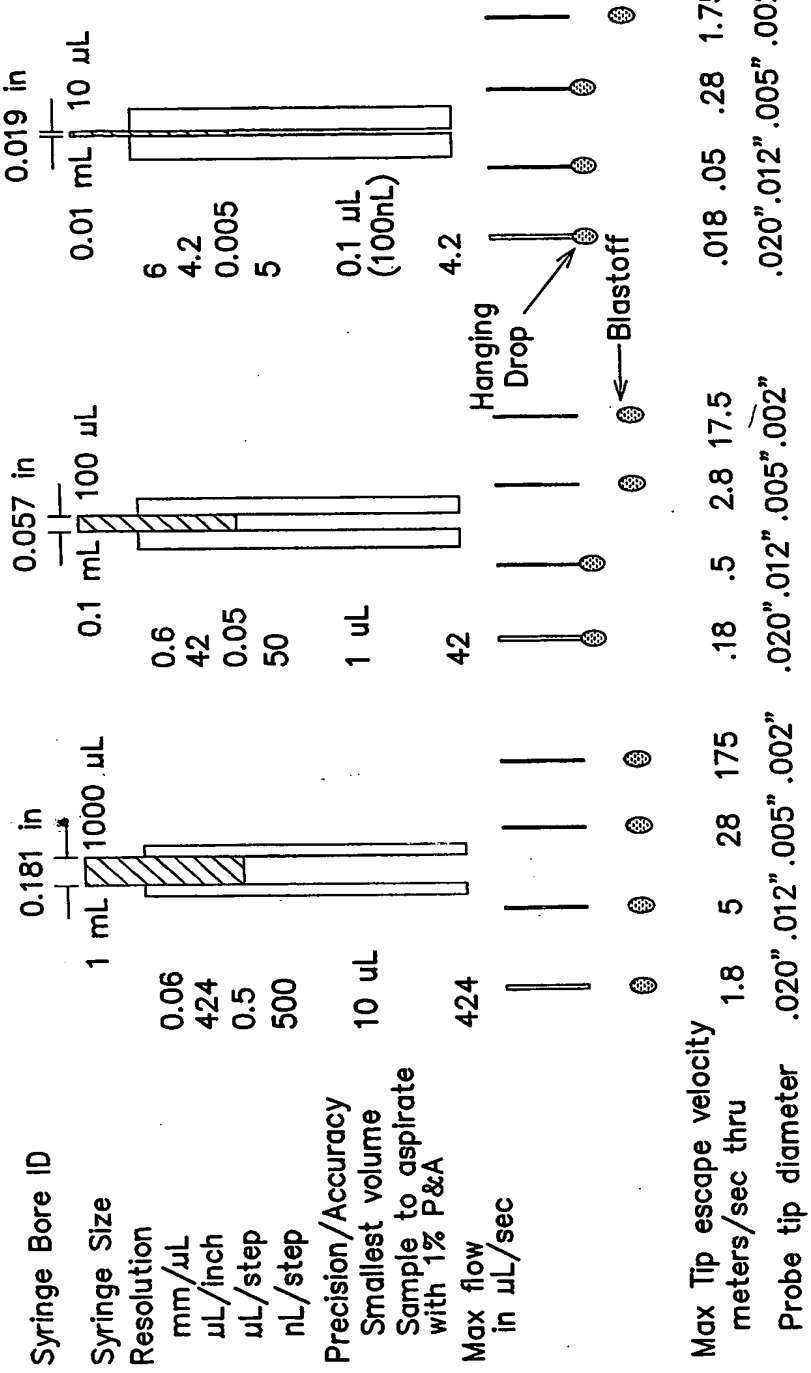
Syringe Bore ID
0.181 in
0.057 in
0.019 in
Syringe Size
1 mL
1000 µL
0.1 mL
100 µL
0.01 mL
10 µL
Resolution
mm/µL
0.06
0.6
6
µL/inch
424
42
4.2
µL/step
0.5
0.05
0.005
nL/step
500
50
5
Precision/Accuracy
Smallest volume
Sample to aspirate with 1% P&A
10 uL
1 uL
0.1 µL (100nL)
Max flow in µL/sec
424
42
4.2
Hanging Drop
Blastoff
Max Tip escape velocity meters/sec thru
1.8
5
28
175
.18
.5
2.8
17.5
.018
.05
.28
1.75
Probe tip diameter
.020" .012" .005" .002"
.020" .012" .005" .002"
.020" .012" .005" .002"

FIG. 8A

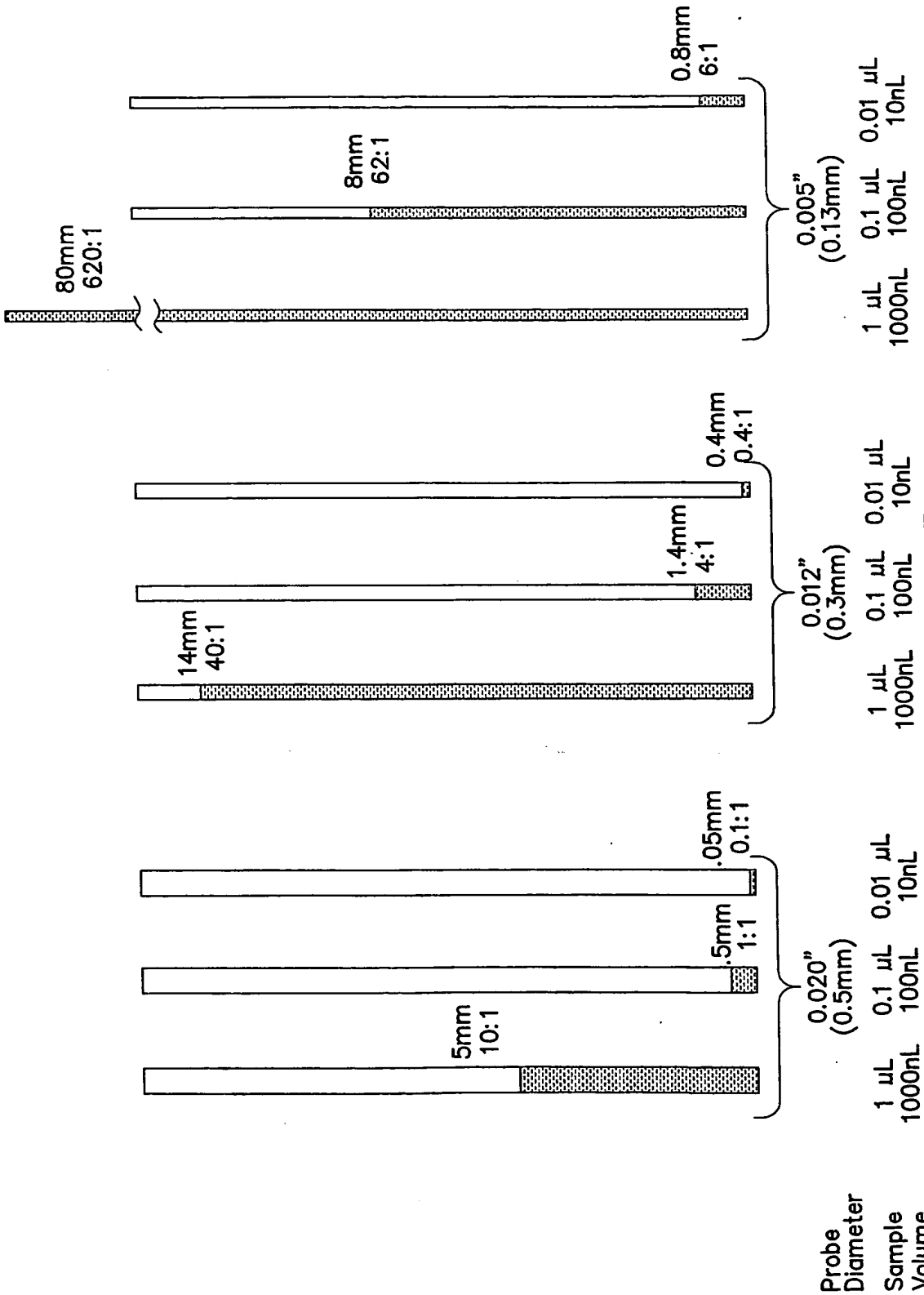

FIG. 8B

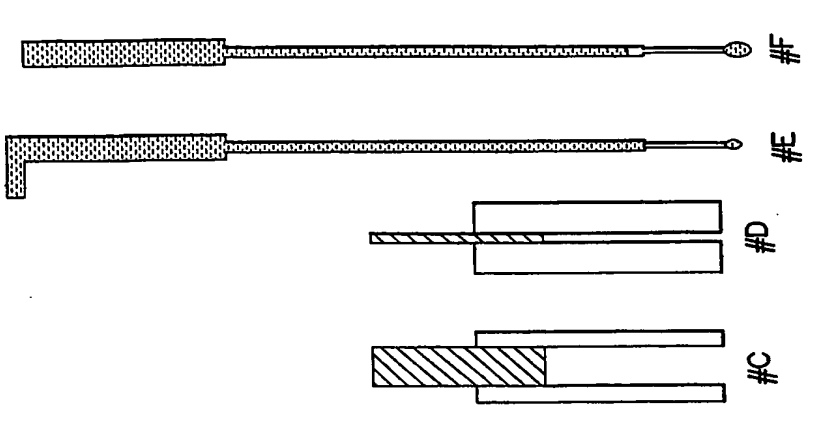

FIG. 8C-3

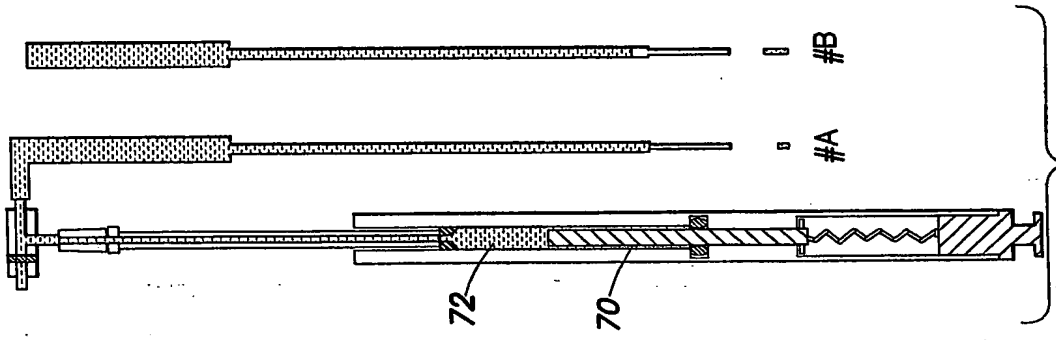

FIG. 8C-2

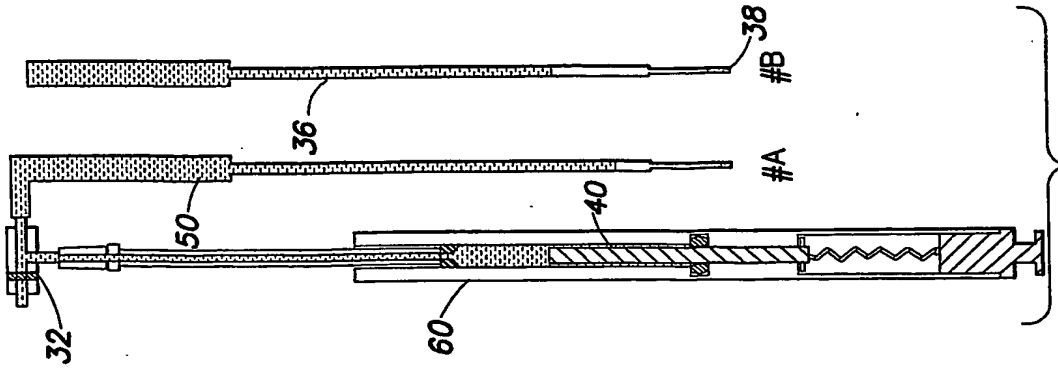

FIG. 8C-1

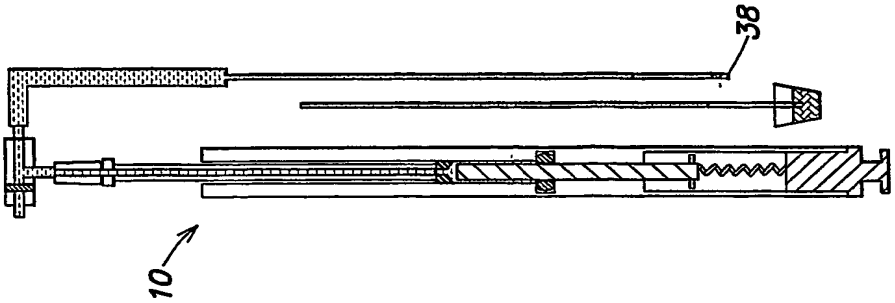

FIG. 9.3

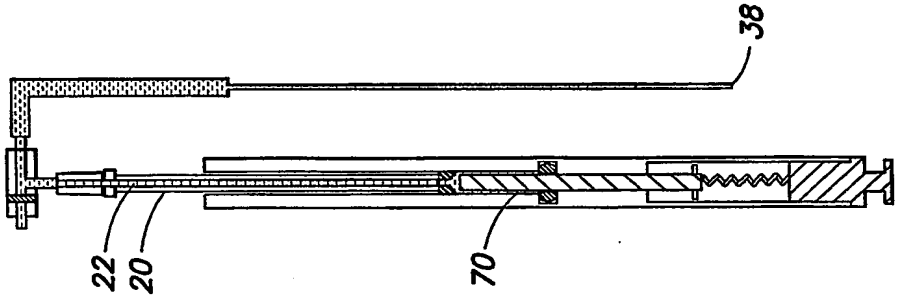

FIG. 9.2

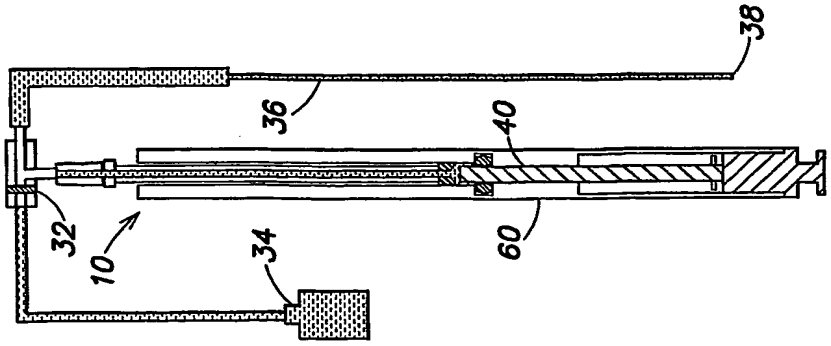

FIG. 9.1

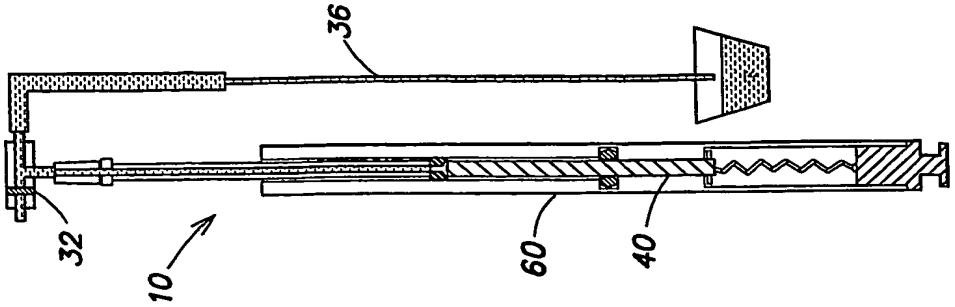

FIG. 9.6

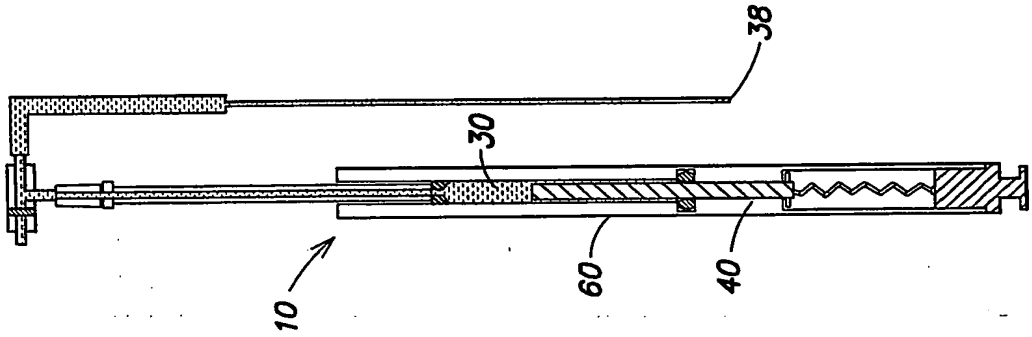

FIG. 9.5

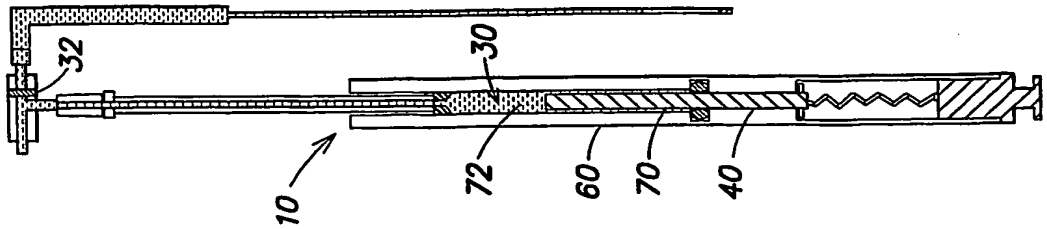

FIG. 9.4

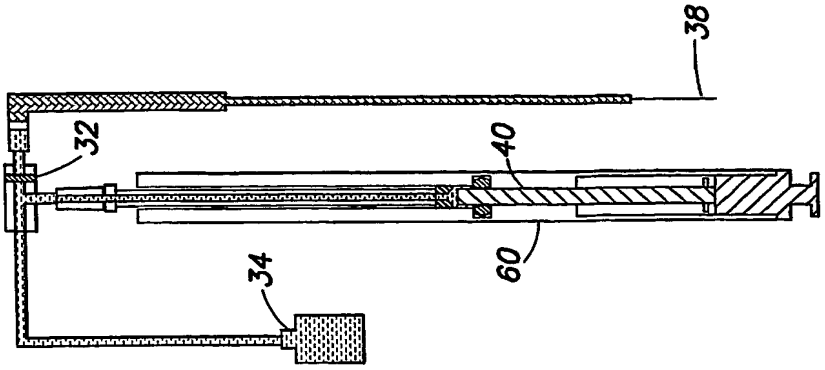

FIG. 10.4

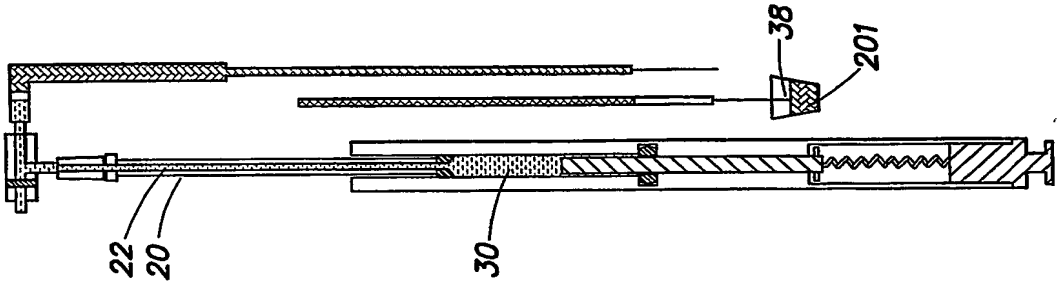

FIG. 10.3

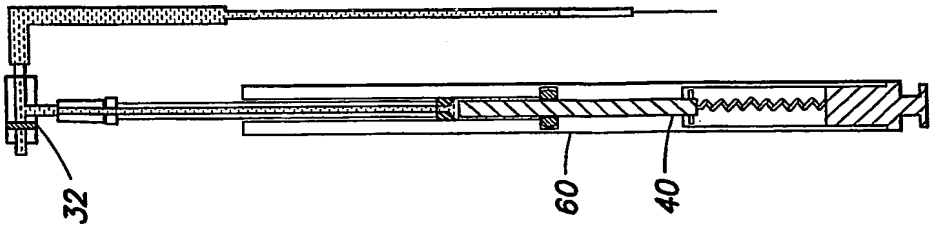

FIG. 10.2

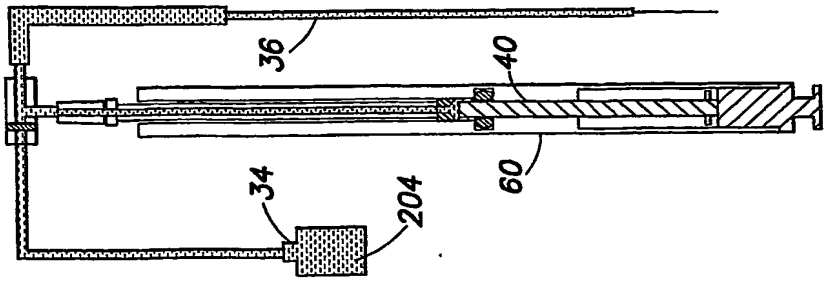

FIG. 10.1

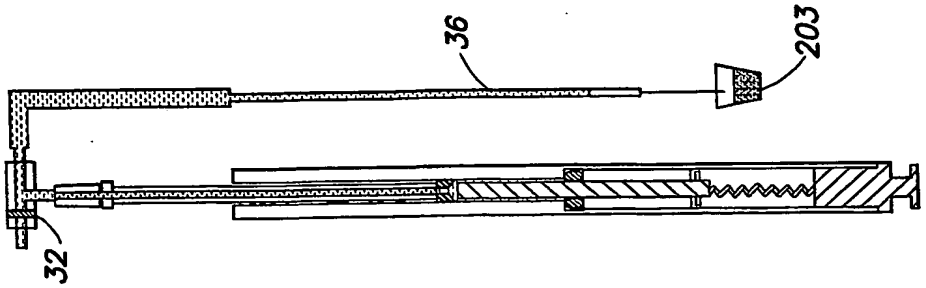

FIG. 10.8

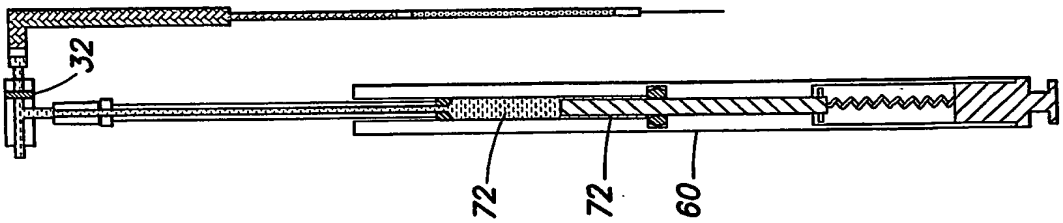

FIG. 10.7

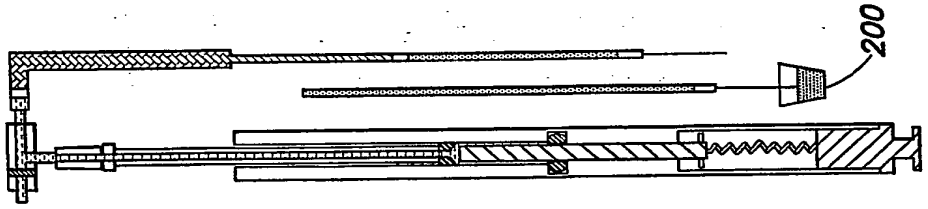

FIG. 10.6

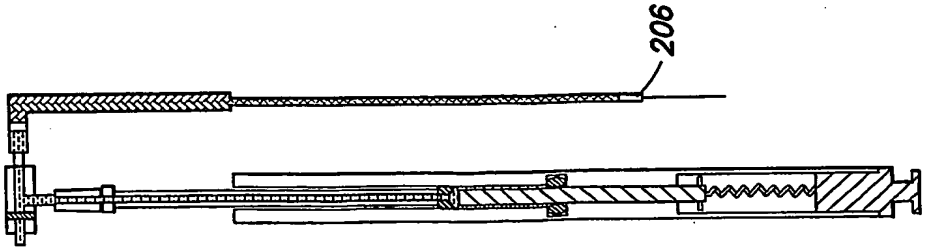

FIG. 10.5

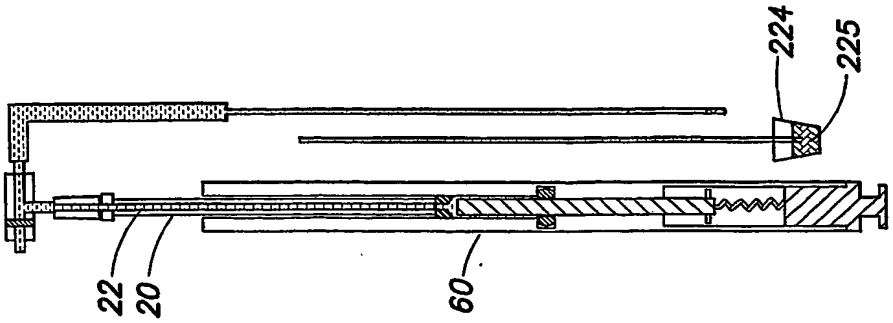

FIG. 11.3

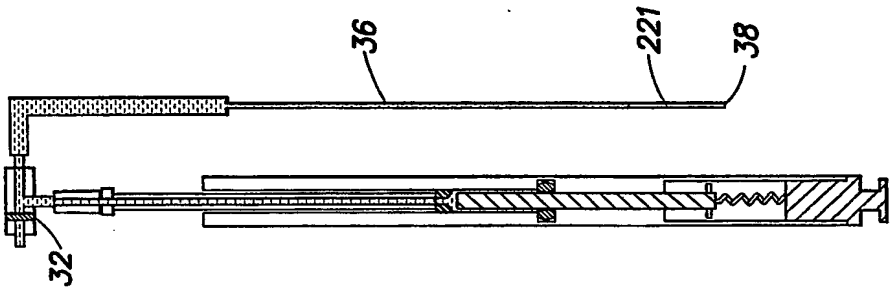

FIG. 11.2

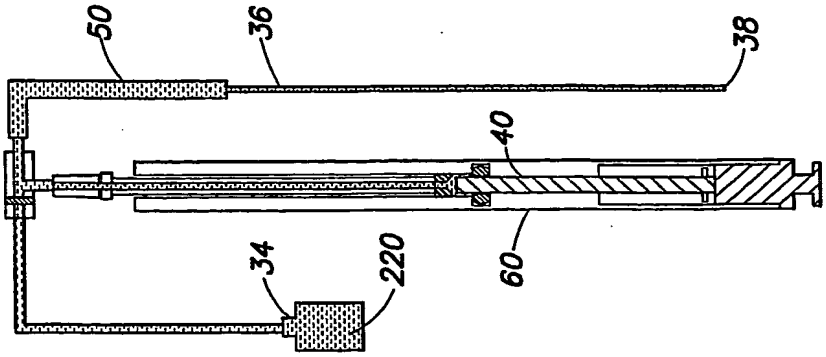

FIG. 11.1

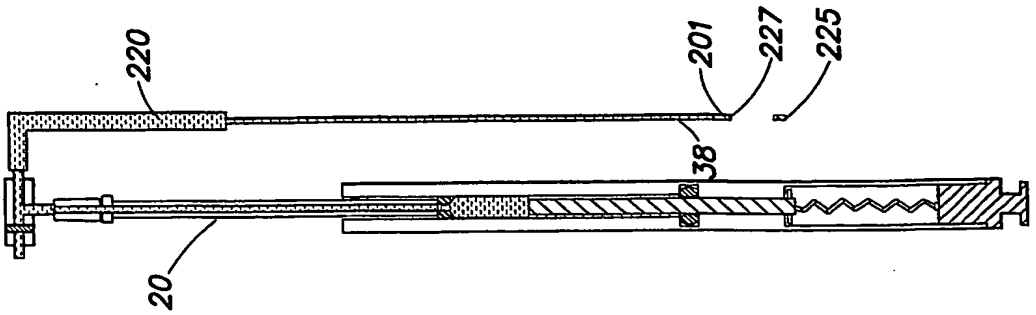

FIG. 11.6

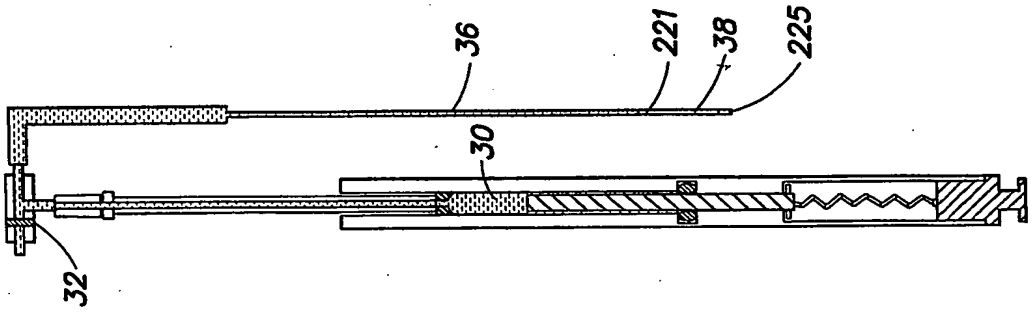

FIG. 11.5

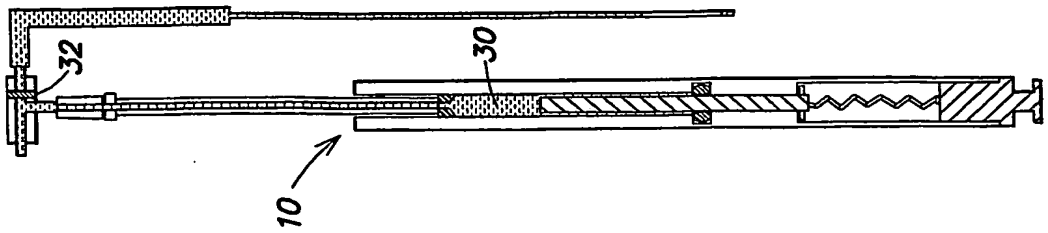

FIG. 11.4

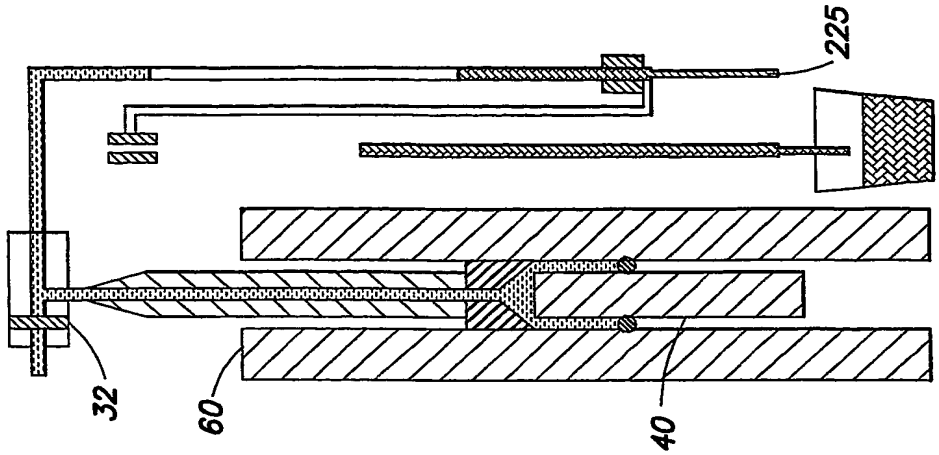

FIG. 12.3

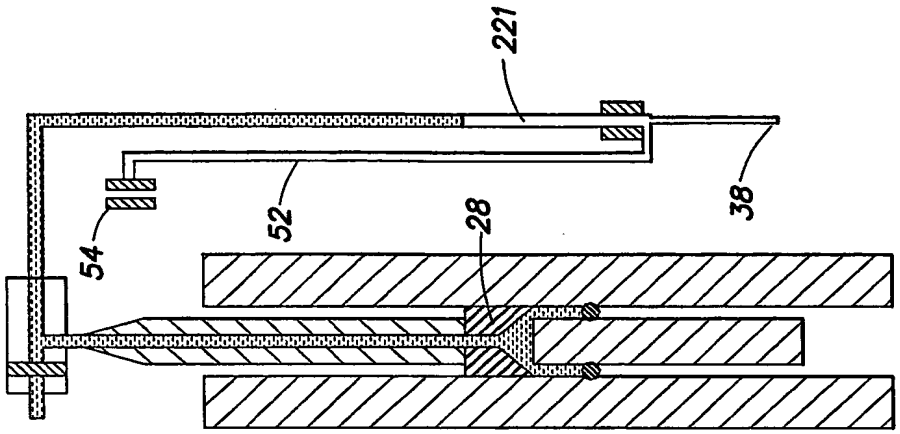

FIG. 12.2

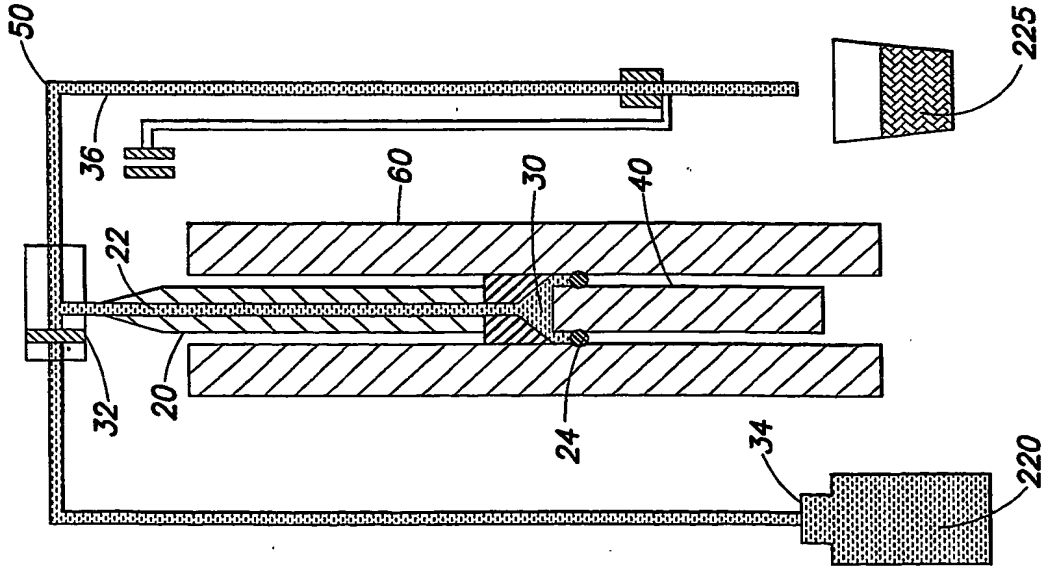

FIG. 12.1

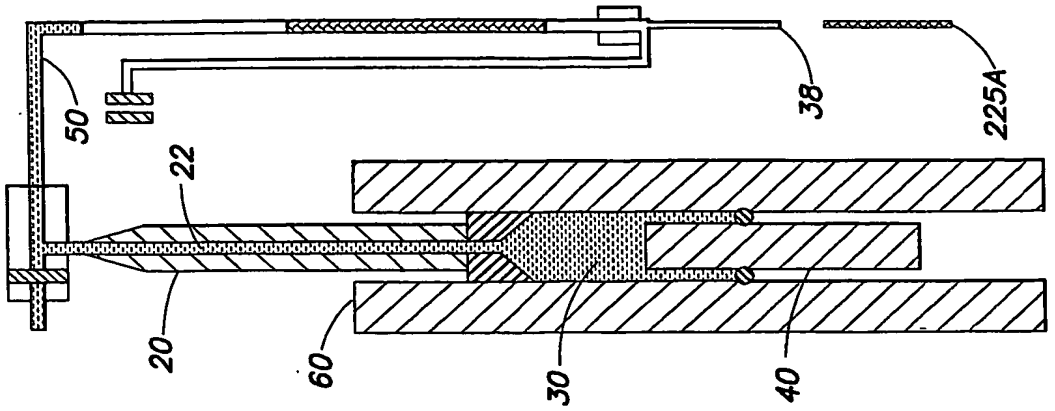

FIG. 12.6

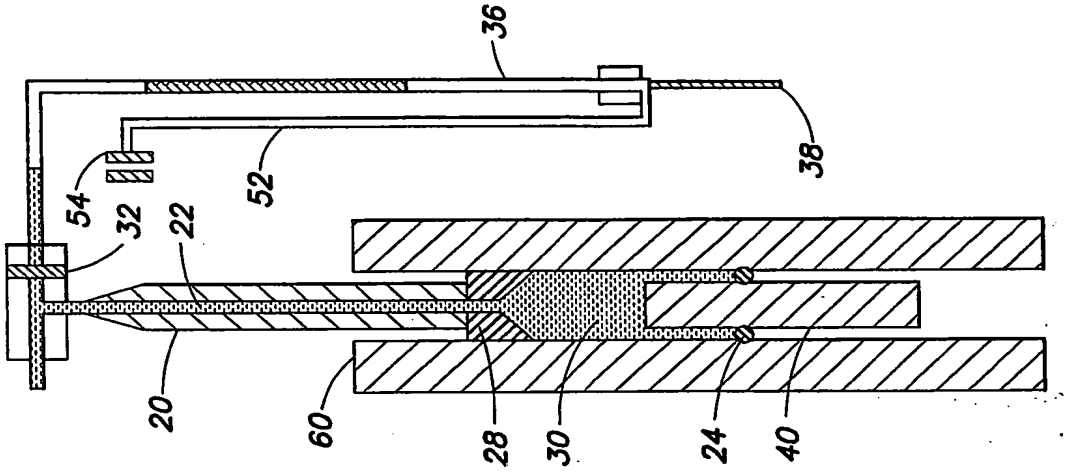

FIG. 12.5

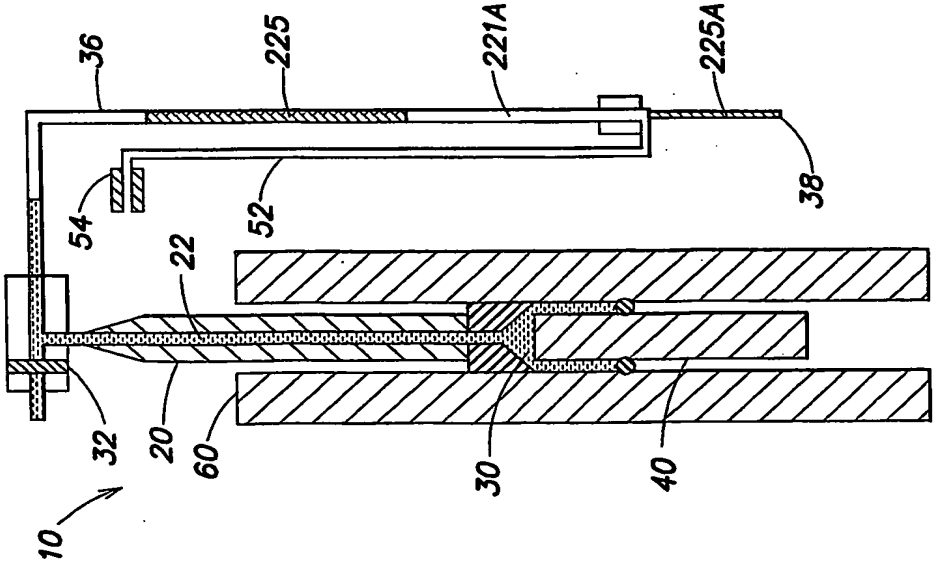

FIG. 12.4

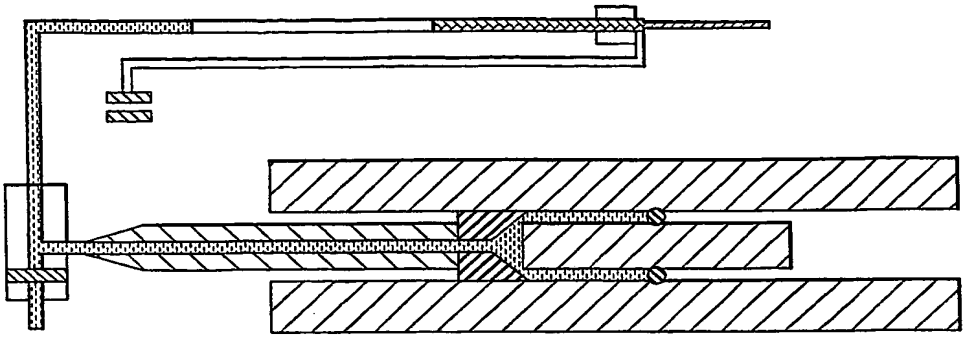

FIG. 12.9

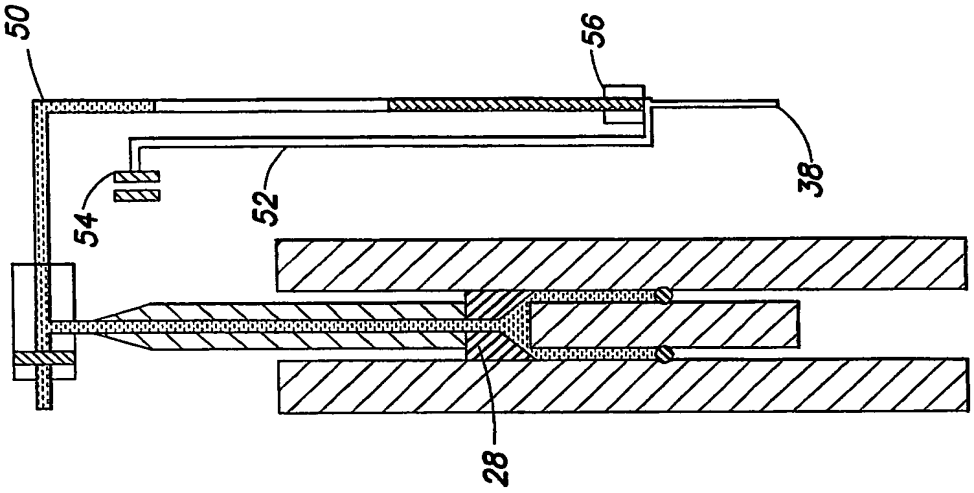

FIG. 12.8

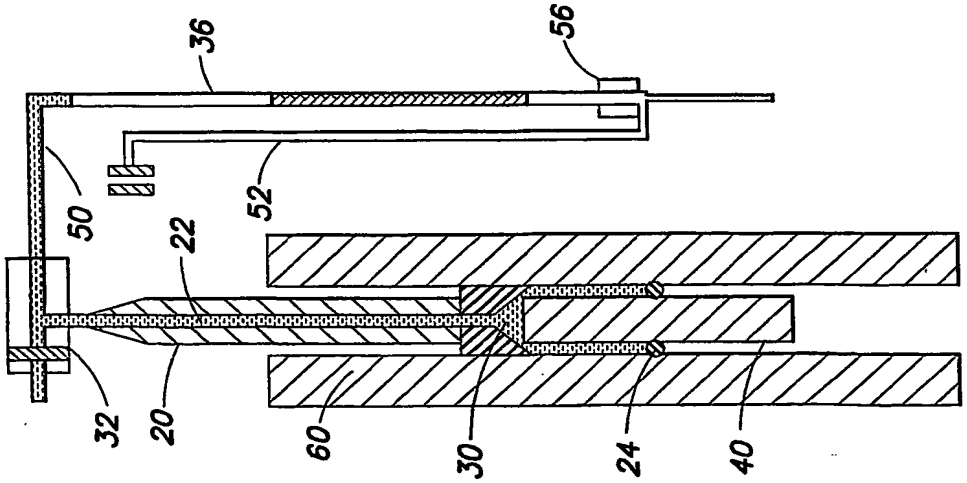

FIG. 12.7

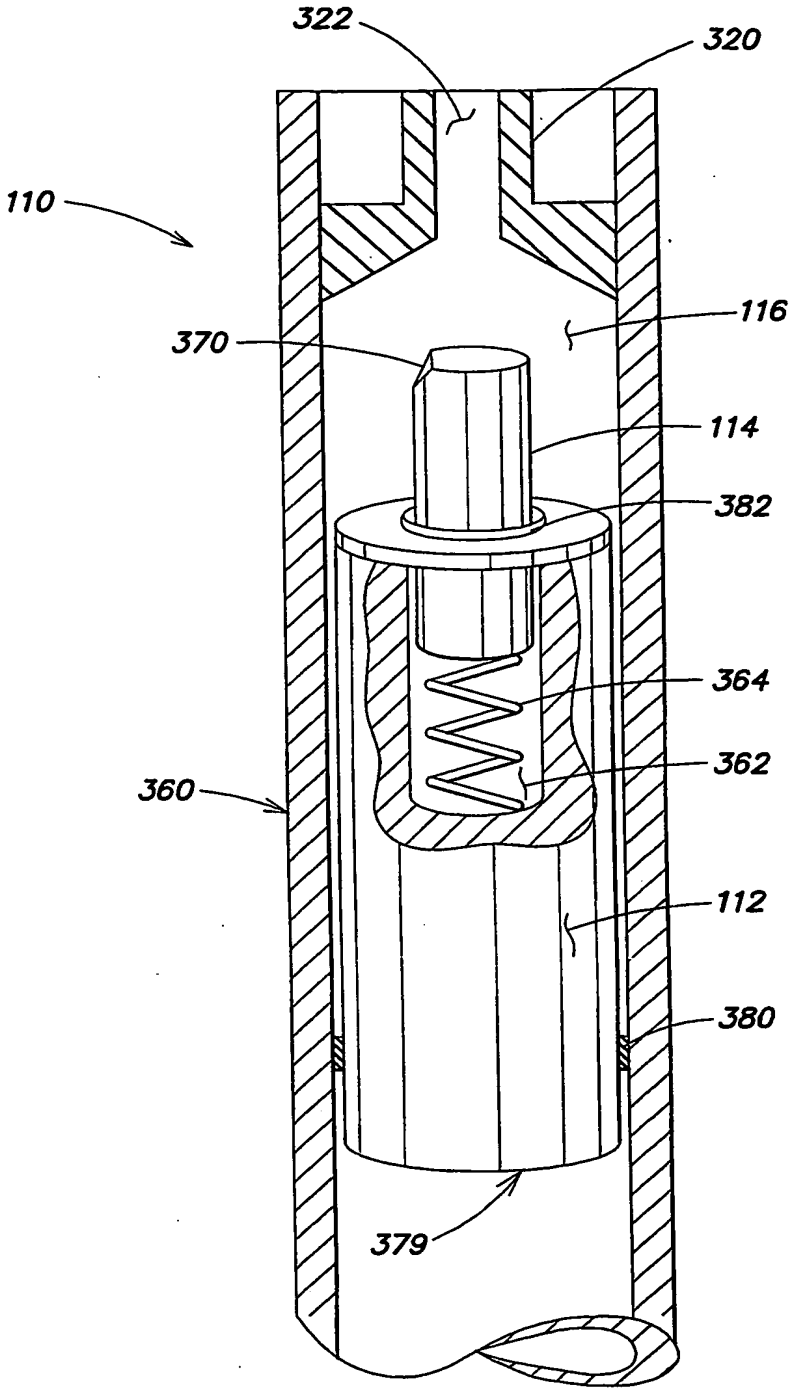

FIG. 13

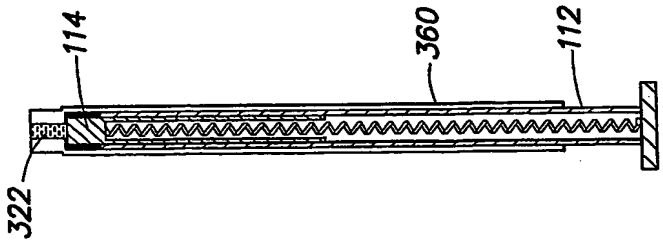

FIG. 14.5

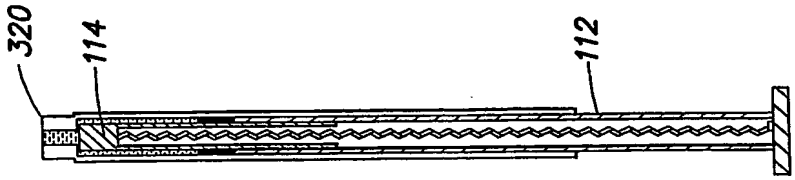

FIG. 14.4

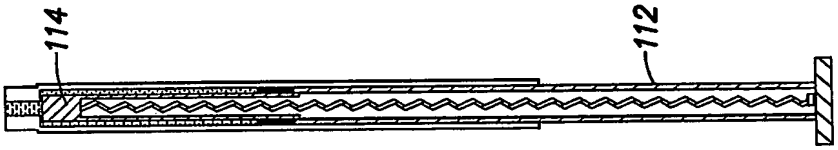

FIG. 14.3

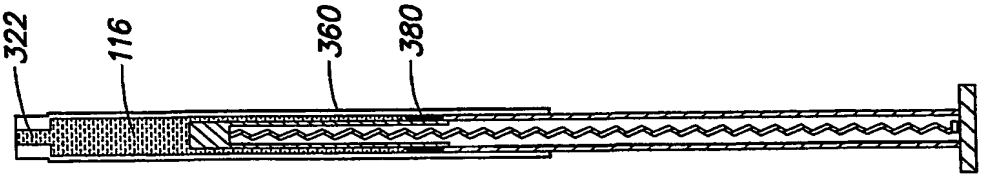

FIG. 14.2

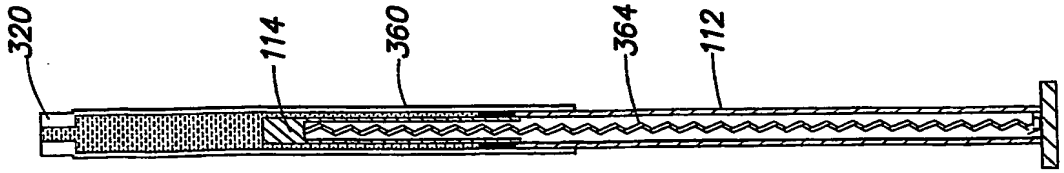

FIG. 14.1